Effectiveness and Cost-effectiveness in Lumbar Spine Surgery

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CHAPTER 1

GENERAL INTRODUCTION

With the growing demand for spinal care, mainly caused by the aging population, unsustainability of spinal care seems inevitable if treatment allocation is not optimized. This thesis is an aggregation of various studies focused on effectiveness and cost-effectiveness of spine surgery.

EPIDEMIOLOGY

Spine-related disorders pose an enormous global healthcare burden, affecting all age groups[1]. Most individuals experience at least one period of spine-related complaints in their lifetime. Disorders related to the spine are responsible for the highest burden of disease in terms of years lived with disability (YLD), and thus contribute to disability more than cancer, cardiovascular diseases, or mental disorders[2]. For example, the burden of disease for back pain has risen at an alarming rate; YLD increased by 54% between 1990 and 2015, and is expected to increase even further in the future[3].

The global prevalence of spine-related complaints is 9.4%, and this increases with age, reaching 19–23% by the age of 80[2,4]. Since 1980, the global population of people older than 60 years has doubled, and this number is expected to double again by 2050[5]. Besides age, spine-related disorders are also associated with a sedentary lifestyle and obesity[3]. Moreover, the global prevalence of obesity, defined as a body-mass index (BMI) of >30 kg/m^2, has nearly tripled since 1975, with over 650 million suffering from obesity in 2016 [6]. Additionally, almost one-third of the global population over 18 years old are not meeting the minimum standards for activity as determined by the World Health Organisation (WHO) in 2020[7]. As a consequence of the ageing population and the increasing prevalence of obesity and physical inactivity, the number of patients with spine-related disorders is rising exponentially[3].

As the prevalence of spine-related disorders increases, so does the number of spinal pathologies that require secondary or tertiary care[8]. Although many patients require conservative treatment, some require surgical treatment[9]. To increase the efficiency and effectivity of care, the selection and profiling of patients with spine-related disorders requiring different types of treatment should be improved[8,10]. In cases where specialist care does not differ from primary care, a referral to a secondary spine centre might not be desirable, and could potentially be avoided.

The first step in the process of optimizing healthcare allocation is to investigate the demographics of patients referred to a secondary spine centre, and the relationship between patient characteristics and allocated treatments. Although disease-specific demographic research is available, studies on demographics of a more general population of patients referred to secondary healthcare with spinal complaints are limited and restricted due to the inclusion of only a handful of parameters such as age, sex and race[11-13]. Insight into specific characteristics of patients requiring specialist care in the form of diagnostics and treatments will drive forward our understanding of this

complex category of patients, and could aid in future decision-making and healthcare allocation.

SURGICAL TREATMENT

Several spine-related disorders require specialist care, and in some cases, surgical intervention. Common spinal pathologies that might require surgical intervention, apart from trauma and malignancy, are lumbar spinal stenosis, herniated disc, degenerative deformities, and spondylolisthesis. Lumbar degenerative disease, which may result in spinal or foraminal stenosis, is caused by disc and facet joint degeneration[14,15]. Spondylolisthesis is the slippage of a vertebra over the underlying vertebra, and can be a result of degeneration or lysis in the pars articularis[16]. Both lumbar spondylolisthesis and degenerative disease can lead to deformity, instability, foraminal stenosis and central spinal canal stenosis. These pathologies can cause serious complaints such as neurogenic claudication, radiculopathy, or axial pain, and have a severe impact on mobility and health-related quality of life[17,18].

Lumbar decompression surgery is a safe and effective intervention to relieve neurological complaints. In cases where it is expected that decompression alone will not be sufficiently effective or will result in instability, decompression combined with fusion is indicated.

The main goal of decompression with lumbar interbody fusion is decompression of neurological structures while maintaining or restoring spinal stability. Lumbar decompression and interbody fusion surgery is one of the most commonly performed instrumented spinal surgeries[19]. Previous studies concerning instrumented spine surgery demonstrate an alarming upward trend in the number of interbody fusion surgeries worldwide[20-26].

SURGICAL TECHNIQUES

Commonly used posterior approaches for lumbar interbody fusion surgery include posterior lumbar interbody fusion (PLIF) and transforaminal lumbar interbody fusion (TLIF)[27]. Although the goal of PLIF and TLIF is comparable, the techniques differ. Thus far, no consensus has been reached on which of these techniques is more effective – both have unique advantages and disadvantages.

PLIF is a technique that was first described in 1944, and has since gained popularity. Since PLIF is the older of the two techniques, most spinal surgeons are well trained in performing this intervention[19]. In PLIF, a midline incision is used, and a medial facetectomy is performed. After removal of the disc and bilateral endplate preparation, two cages are inserted bilaterally. This approach provides excellent visualization of anatomic structures, including the nerve roots[28]. Despite these advantages, PLIF has various disadvantages inevitably associated with the approach. Namely, because of the

bilateral approach to the intervertebral disc and bilateral insertion of cages, PLIF is associated with iatrogenic injury to the paravertebral musculature and soft tissue. Consequently, this might lead to delayed recovery[29]. Injury to the nerve root or perineural iatrogenic fibrosis are other potential complications, leading to chronic complaints or impairment[30].

The TLIF technique was developed to reduce the iatrogenic injury associated with PLIF. In TLIF, the intervertebral space is approached through a unilateral transforaminal route, as opposed to the bilateral approach in PLIF. Moreover, ligamentous structures that provide stability to the spine are preserved[31]. The disadvantages of TLIF are comparable to those of PLIF, and are mainly a consequence of iatrogenic injury associated with the approach. Although the complications in PLIF and TLIF are similar, it has been suggested that TLIF is superior to PLIF due to a lower incidence of complications, less blood loss, and shorter OR time and length of hospital stay, while maintaining comparable clinical outcomes[32].

Over the last decade, minimally invasive variations of these open techniques are gaining popularity. The most common of these alternatives is the minimally invasive TLIF (MITLIF). In MITLIF, decompression and cage insertion are performed through tubular retractors, followed by percutaneous posterior pedicle screw fixation. Although the long-term effectiveness of MITLIF is comparable to open TLIF, several studies found that MITLIF was associated with even fewer complications and blood loss, and a shorter length of hospital stay compared to open TLIF. It is assumed that these benefits are the result of less soft-tissue damage, while maintaining the advantages of the posterior approach[33-37].

Since the different approaches are mostly comparable in terms of effectivity and safety, choices are frequently based on surgeons' preferences or availability. As costs might become a limiting factor in spine surgery in the future, comparing the cost-effectiveness of these approaches will provide a relevant parameter that can aid in surgical decision-making.

COSTS & SOCIETAL IMPACT

As mentioned previously, the prevalence of spinal pathologies requiring surgical treatment is increasing at an alarming rate. This also leads to an increase in costs[38,39].

In terms of healthcare economics, costs are divided into two major categories: direct and indirect costs. The former are costs that are a direct result of a pathology or treatment, such as inpatient and outpatient care, physician services, ancillary services, medication, and devices. Indirect costs refer to the economic value of any consequences of a pathology or treatment that cannot be considered as direct costs. For example, indirect costs include change in productivity, forgone leisure time, and changes in productivity by family or informal caregivers. Economic evaluations can be performed from a

healthcare or hospital perspective, usually analyzing direct costs, or from a broader societal perspective, incorporating both direct and indirect costs[40].
Within the field of spine surgery, both direct and indirect costs are of significance. Direct costs are increasing not only because of the quantity of performed surgeries, but also because of increasing costs per surgery as a result of implementations of modern technology and the use of novel instruments and implants[41]. Although the number of instrumented spine surgeries showed a 2.4-fold increase between 1998 and 2008, the associated direct costs increased by 7.9-fold in this period. In the period between 2004 and 2015, the number of instrumented spine surgeries showed a 1.6-fold increase, while associated direct costs increased by 2.8-fold[20,21]. In addition to direct costs, indirect costs of spinal complaints – mainly driven by loss of productivity by patients and informal caregivers[42] – pose a significant economic burden to society. American and European studies prospectively comparing lumbar interbody fusion surgeries have shown that indirect costs account for one-third to half of the total costs[43-45].

ECONOMIC EVALUATIONS IN SPINE SURGERY

With the rapid growth of healthcare expenditure, the interest in economic evaluations has risen over recent decades. Economic evaluations focus on the cost-benefit tradeoff of interventions, and investigate not only the effect and utility, but also the associated costs. Economic evaluations can be used to compare the cost-effectiveness of new interventions, or to investigate how existing interventions perform in terms of economic efficiency. Considering that rising global healthcare expenses are reaching unsustainable proportions, economic evaluations are now more important than ever.
The value of economic evaluations is progressively renowned, as reflected by the observed increase in studies mentioning costs and cost-effectiveness in the last decade[46-48]. However, due to an enormous diversity in interventions, outcomes, and cost calculations, comparing the findings of such studies is very difficult. Additionally, since healthcare and reimbursement systems vary greatly between countries, calculation and valuation of costs in a manner that enables international comparability is challenging[46,49-52]. Despite the increase in the number of economic evaluations in spine surgery over the last decade, methodological heterogeneity may impair comparability of results.
General international, national, and regional recommendations for the conduct of economic evaluations are available[53-55]. However, considering the heterogeneity in the conduct and reporting of economic evaluations in spine surgery, these general guidelines might be insufficient. This likely arises from the fact that general guidelines do not incorporate disease- and topic-specific recommendations by nature. Hence, a disease-specific guideline as a supplement to general guidelines could be beneficial for improving the quality and comparability of economic evaluations. Several disease-specific guidelines regarding the conduct of economic evaluations are available, however

not in the field of spine surgery[56-58]. Within the literature, it is obvious that many authors in this field share the opinion that more uniformity is desirable[50-52].

THESIS OUTLINE

This thesis on the effectiveness and cost-effectiveness in lumbar spine surgery is subdivided into three overarching topics. The first topic focusses on the characteristics of patients referred to a secondary spine centre. The second topic, comprising Chapters 3, 4 and 5, centers around the clinical effectiveness and cost-effectiveness of lumbar interbody fusion surgery. The third topic is on economic evaluations in spine surgery, addressed in Chapters 6, 7 and 8.

In **Chapter 2**, we review a one-year cohort of patients with spinal-related complaints referred to a secondary spine centre, and evaluate symptoms, diagnostic methods, diagnosis, and treatment allocation. The aim of this study was to provide a comprehensive understanding of the resources used for patients that were referred to a specialized secondary spine centre.
In order to directly compare the effectiveness and safety of the most commonly used approaches for lumbar interbody fusion, we conducted a randomized controlled trial directly comparing PLIF and TLIF. The results of this trial one year after surgery are described in **Chapter 3**.
In **Chapter 4**, we describe a qualitative process evaluation study in which we aimed to gain insight into the full process surrounding lumbar fusion surgery in five Dutch hospitals. Steps in the process were evaluated by patients, informal caregivers, and healthcare professionals. The ultimate goal of the study was to provide qualitative data that can be used to optimize the healthcare process of lumbar interbody fusion surgeries.
To compare the cost-effectiveness of commonly performed open lumbar interbody fusions to the minimally invasive alternative, we conducted a systematic review and meta-analysis, which is presented in **Chapter 5**. In this systematic review, previous literature concerning costs and cost-effectiveness of the open TLIF were compared with MITLIF in patients with lumbar spondylolisthesis or degenerative disease.
Chapter 6 describes a study protocol for a Delphi-consensus study aimed at providing an evidence-based guideline for economic evaluations in spine surgery. As a part of this study, we performed a systematic review and qualitative analysis of the currently available cost-effectiveness literature in the field of spine surgery. This work is presented in **Chapter 7**. Besides providing a complete, up-to-date overview of current methodology and quality of cost-effectiveness research in spine surgery, this study also aimed to identify the disparity in the current practice and develop adequate recommendations to assess these gaps.

In **Chapter 8**, we describe the methodologic properties and results of the Delphi study, and provide validated disease-specific recommendations for the design, conduct and reporting of trial-based economic evaluations in spine surgery.

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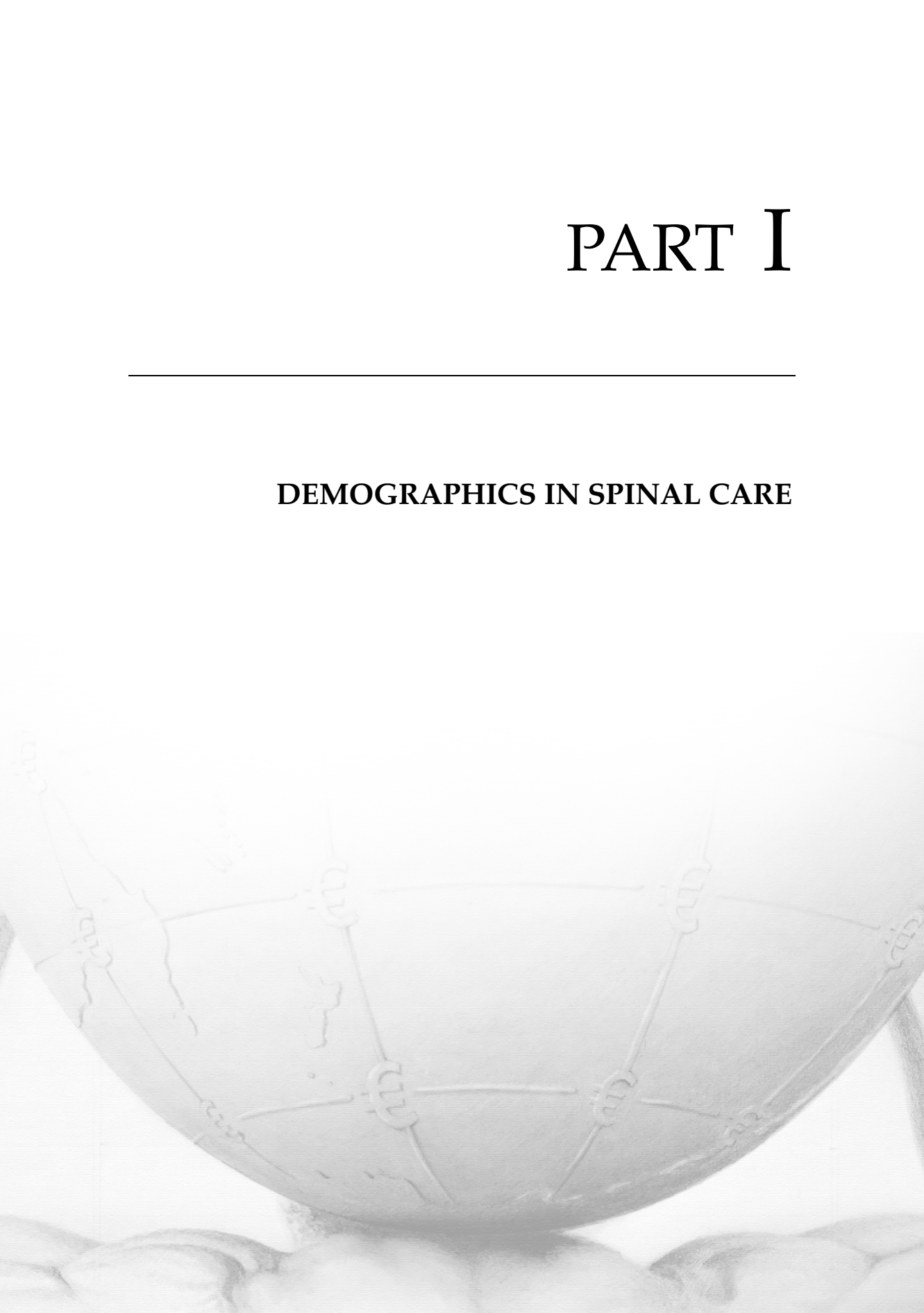
PART I

DEMOGRAPHICS IN SPINAL CARE



CHAPTER 2

REFERRALS, SYMPTOMS AND TREATMENT OF PATIENTS REFERRED TO A SECONDARY SPINE CENTER – HOW CAN WE HELP?

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ABSTRACT

Introduction
Spinal disorders are amongst the conditions with the highest burden of disease. To limit the increase of related healthcare-related costs in the ageing population, the selection of patients with spinal disorders requiring different types of care should be optimized. The first step is to investigate the characteristics of these patients and the relationship with the treatment.

Research question
The aim of this study was to provide a comprehensive understanding of utilized resources for patients referred to a specialized spinal health care center.

Methods
This study describes the characteristics of 4855 patients referred to a secondary spine center.

Results
The mean age was 58.1, 56% of patients was female, and the mean BMI was 28. 28% of patients used opioids. Mean self-reported health status was 53.3 (EuroQol 5D Visual Analogue Scale) and pain ranged from 5.8 to 6.7 (Visual Analogue Scale neck/back/arm/leg). 67.7% of patients received additional imaging. Surgical treatment was indicated for 4.9% of patients. The majority (83%) of non-surgically treated patients received out-of-hospital treatment. 25% of patients received no additional imaging or in-hospital treatment.

Conclusion
The vast majority of patients received non-surgical treatments. We observed that ~10% of patients did not receive in-hospital imaging or treatment and had acceptable or good questionnaire scores at the time of referral. These findings suggest that there is potential for improvement in efficacy of referral, diagnosis and treatment. Future studies should aim to develop an evidence-base for improved patients' selection for clinical pathways. The efficacy of chosen treatments requires investigation of large cohorts.

1. INTRODUCTION

The majority of people experiences at least one episode of spine-related disorders in their lifetime. Spine related complaints are an enormous global healthcare burden[1]. As an example, back pain is amongst the conditions with the highest burden of disease in terms of years lived with disability (YLD)[2].The prevalence in adults increases to 19-23% by the age of 80[3]. Since 1980, the global population of people older than 60 years has doubled and this number is expected to double again by 2050[4-6]. Due to ageing of the population, the number of patients with spinal disorders increases exponentially. The increasing incidence of spinal disorders consequently leads to åan increase in healthcare-related costs[7,8].

Continuously, health care systems have to cope with less resources per patient. Therefore, it is pivotal to continuously evaluate resource utilization in health care pathways for the characteristics of patients, the volume of diagnostics and the specificity of treatments, and ultimately the appropriateness of referrals from primary to specialized care. The first step is to investigate the characteristics of this population and the relationship between these characteristics and indicated treatments.

Currently, patients with spinal disorders are often referred to a secondary spine center, while it is unclear what resources of specialized healthcare, e.g., imaging, specialized treatments, expert opinion, are utilized and required. In many of cases, no anatomical substrate responsible for the patients' complaints is found and the majority receives conservative treatment. Some disease-specific demographic research is available, reporting an increase of expenditures for all spine-related inpatient care and an increasing demand for out-patients spinal care[7,9]. One study focussed on specific biopsychosocial characteristics of patients suffering from chronic low back pain and concluded that a multidisciplinary biopsychological approach is needed for this complex category of patients[10]. More comprehensive information about symptoms, diagnostics, or treatment is lacking in these studies.

The aim of this study was to provide a comprehensive understanding of utilized resources for patients referred to a specialized spinal health care center. We therefore assessed patient characteristics, reported symptoms, diagnostic methods, diagnoses, and treatments in a one-year cohort of patients with spinal disorders referred to the secondary spine center of Zuyderland Medical Center, the Netherlands.

2. MATERIALS AND METHODS

2.1. Study design

A retrospective cohort study using prospectively collected data of all patients that were referred to the secondary spine-center in 2019 was conducted in Zuyderland Medical

Center. This study has been approved by the local institutional medical ethical committee (Medical Research Ethics Committee Zuyderland, METCZ20210030).
The first aim of the study was to provide a comprehensive characterization of all patients, their symptoms and diagnosis. The second aim of this study was to perform an in-depth analysis of resource utilization in the specialized spine-center for a representative subgroup of patients (~20%).
Patient characteristics were assessed by demographics, reported symptoms, and diagnosis. Resource utilization was defined as receiving a specialist's consultation (all patients), having additional imaging, or receiving specialized treatment.

2.2. Study population and selection

The study population consists of all adult patients newly referred to the secondary spine center in 2019. This study was carried out within the Dutch healthcare system, in which the general practitioner functions as a gatekeeper for secondary healthcare; patients cannot consult a medical specialist without a referral from the general practitioner. The only exclusion criterium was documented objection to participate in scientific research.

2.3. Patients, symptoms and diagnosis

An independent hospital data specialist conducted a search in the electronic patients records for the year 2019, using reimbursement codes. Patient demographics, symptoms and diagnoses are available in the electronic patient records. Symptoms are assessed by questionnaires, who every patient is inquired to complete before consultation. Diagnosis codes were clustered into diagnosis-groups: 1) spinal complaints without an evident anatomical substrate, 2) complaints as a result of a herniated disc, or radiculopathy in the thoracolumbar region and radiculopathy in the thoracolumbar spine, 3) spinal stenosis, 4) cervical spinal pathology with neurological complaints, and 5) other diagnoses.

2.4. Imaging, treatment and analgesia

Imaging diagnostics, treatment allocation, and analgesics use were manually extracted from the hospital records by RD and DN. Because of the immense workload arising from manual extraction of this data, we decided to collect data for a subgroup of ~20% of patients (N=1008).
A comprehensive overview of the type of collected data can be found in Table 2.1.

Table 2.1 - Overview of extracted data.

Data	Outcome	Variable
Patient characteristics	Age	Years
	Gender	M / F
	BMI	Kg/m²
	Smoking	Yes / No
	Duration of symptoms	Weeks
	Analgesic use	Yes / No (If yes ✍ paracetamol/NSAID/opioids/ neuropathic pain medication)
Questionnaires	EQ-5D VAS	Score: 0-100 (High score equals better health status) Acceptable: >70. Good: >80 [11]
	RDQ	Score: 0-24 (High score equals more disability) Acceptable: <6. Good <4 [12]
	Tampa Scale of Kinesiophobia	Score: 17-68 (High score equals more kinesiophobia) No kinesiophobia: <37 [13]
	VAS back/neck/leg/arm	Score: 0-10 (High score equals more pain) Acceptable: <5. Good: <1 [14]
	ÖREBRO	Score 0-210 (High score equals more pain) Acceptable: <130. Good: <105 [15,16]
Additional diagnostics	Additional imaging	MRI / CT
	Other additional diagnostics	EMG / Diagnostic nerve block
Diagnosis Codes	Diagnosis-Groups	Spinal complaints without an evident anatomical substrate Complaints as a result of a herniated disc, or radiculopathy in the thoracolumbar region and radiculopathy in the thoracolumbar spine Spinal stenosis Cervical spinal pathology with neurological complaints Other diagnoses
Treatment data	Intervention	Surgery (and type of surgery, e.g., interbody fusion, interlaminar decompression, discectomy, laminectomy, foraminotomy, sacroiliac joint fusion) / Conservative (and type of conservative treatment, e.g., physical therapy, pain treatment, expectative, rehabilitation, return to general practitioner)

Abbreviations: BMI: Body Mass Index, EQ-5D VAS: EuroQol 5D Visual Analogue Scale, MD: Missing Data, ÖREBRO: Örebro Musculoskeletal Pain Screening Questionnaire, RDQ: Roland Disability Questionnaire, TAMPA: Tampa Scale of Kinesiophobia, VAS: Visual Analogue Scale.

2.5. Data analysis

Data was collected into an anonymised database. P values of <0.05 were considered significant and the analyses were carried out using IBM SPSS statistics 26[17].
Descriptive statistics (means ±SD, frequencies as %) were performed. To determine whether the subgroup of the in-depth-cohort was representative of the total cohort, we compared their characteristics with the total group. Data was normally distributed and was hence compared by independent samples t-tests and Chi-Square tests for continuous and categorical variables, respectively.

3. RESULTS

3.1. Patient characteristics

A total of 4855 patients were referred to the secondary spine center at Zuyderland Medical Center the Netherlands in 2019. None had documented objection to participate in research. Patient characteristics are presented in Table 2.2. Except for age, the subgroup of patients was comparable to the full cohort.

Table 2.2 - Patient characteristics.

Name	Factor	Outcome (N=4855)	%MD	Outcome (N=1008)	%MD
Personal and demographic	Age	58.1 ± 15.4	0%	60.0 ± 14.1	0%
	Gender (male/female)	2146/2709 (44/56%)	0%	445/563 (44/56%)	0%
	Body Mass Index (kg/m²)	28.1 ± 5.3	76%	28.2 ± 5.4	78%
	Overweight, Obesity	41%, 31%		36%, 33%	
	Smoking	-	-	34.1% Yes 65.9% No	59%
	Duration of symptoms	-	-	<6w 12.5% 6w-3m 17.9% 3m-6m 14.6% 6m-12m 14.0% >12m 35.0%	6%
Analgesics use	Opioids	-	-	27.9%	0%
	NSAIDs	-	-	25.7%	0%
	Paracetamol	-	-	29.7%	0%
	Co-analgesics	-	-	6.9%	0%
	None	-	-	22.8%	0%
	Not reported	-	-	18.3%	0%

Abbreviations – MD: Missing Data, NSAID: Non-Steroidal Anti-Inflammatory Drug.

3.2. Questionnaire scores

Questionnaire scores are summarized in Table 2.3 and Figure 2.1. On average, completion rate of questionnaires was 75%. There were no statistically significant differences between the total cohort and the subgroup of patients. Self-reported health status at first referral was 53.3 ± 20.2 (EuroQol 5D Visual Analogue Scale), musculoskeletal pain was 121.8 ± 30.1 (Örebro Musculoskeletal Pain Screening Questionnaire), disability was 14.3 ± 5.3 (Roland Disability Questionnaire), kinesiophobia was 41.1 ± 8.0 (Tampa Scale of Kinesiophobia), and pain ranged from 5.8 to 6.7 (Visual Analogue Scale neck, back, arm and leg).

Table 2.3 – Questionnaire scores.

Factor	Outcome (N=4855)	%MD	Outcome (N=1008)	%MD
EQ-5D VAS (0-100)	53.3 ± 20.2	15%	53.1 ± 19.5	13%
RDQ (0-24)	14.3 ± 5.3	37%	14.4 ± 5.1	31%
TAMPA (20-68)	41.1 ± 8.0	24%	41.1 ± 8.2	17%
VAS Back (0-10)	6.7 ± 2.3	25%*	6.6 ± 2.4	22%*
VAS Leg (0-10)	5.8 ± 2.8	25%*	5.9 ± 2.7	22%*
VAS Neck (0-10)	6.4 ± 2.6	25%**	6.5 ± 2.6	19%**
VAS Arm (0-10)	5.9 ± 2.8	25%**	5.9 ± 2.8	19%**
ÖREBRO	122 ± 30	57%	121 ± 30	56%

Data are presented as means +/- SD. Abbreviations – EQ-5D VAS: EuroQol 5D Visual Analogue Scale, MD: Missing Data, ÖREBRO: Örebro Musculoskeletal Pain Screening Questionnaire, RDQ: Roland Disability Questionnaire, TAMPA: Tampa Scale of Kinesiophobia, VAS: Visual Analogue Scale
There were no statistically significant differences between groups.
* The percentage reflects the missing data for patients referred with complaints of the thoracolumbar spine.
** The percentage reflects the missing data for patients referred with complaints of the cervical spine.
The percentages of missing data for all other questionnaires reflect the total cohorts of patients (4855 and 1008 respectively)

3.3. Additional imaging

All patients referred to the spine center received conventional radiographic imaging of the spinal region for which they were referred. Of the 1008 patient-subgroup, 682 (67.7%) received additional imaging diagnostics. Of these patients, 638 (93.5%) received an MRI-Scan, and 113 (16.6%) received a CT-Scan.

3.4. Diagnosis

Among the referred subgroup of patients, 315 (31%) were diagnosed with spinal complaints without evident anatomical substrate, 332 (33%) with a herniated nucleus pulposus or radiculopathy in the thoracolumbar region, 110 (11%) with spinal stenosis, and 75 (7%) with cervical pathology with neurological complaints. 176 (17%) patients received other diagnoses (for example peripheral mononeuropathy, coxarthrosis, musculoskeletal pathology of the shoulder, etc.).
The use of additional imaging diagnostics varied between diagnosis-groups (Figure 2.2). For the diagnoses 'No anatomic substrate' or 'Other', additional imaging was utilized in 50% of cases, while for other diagnoses, the utilization of MRI and CT exceeded 90%.

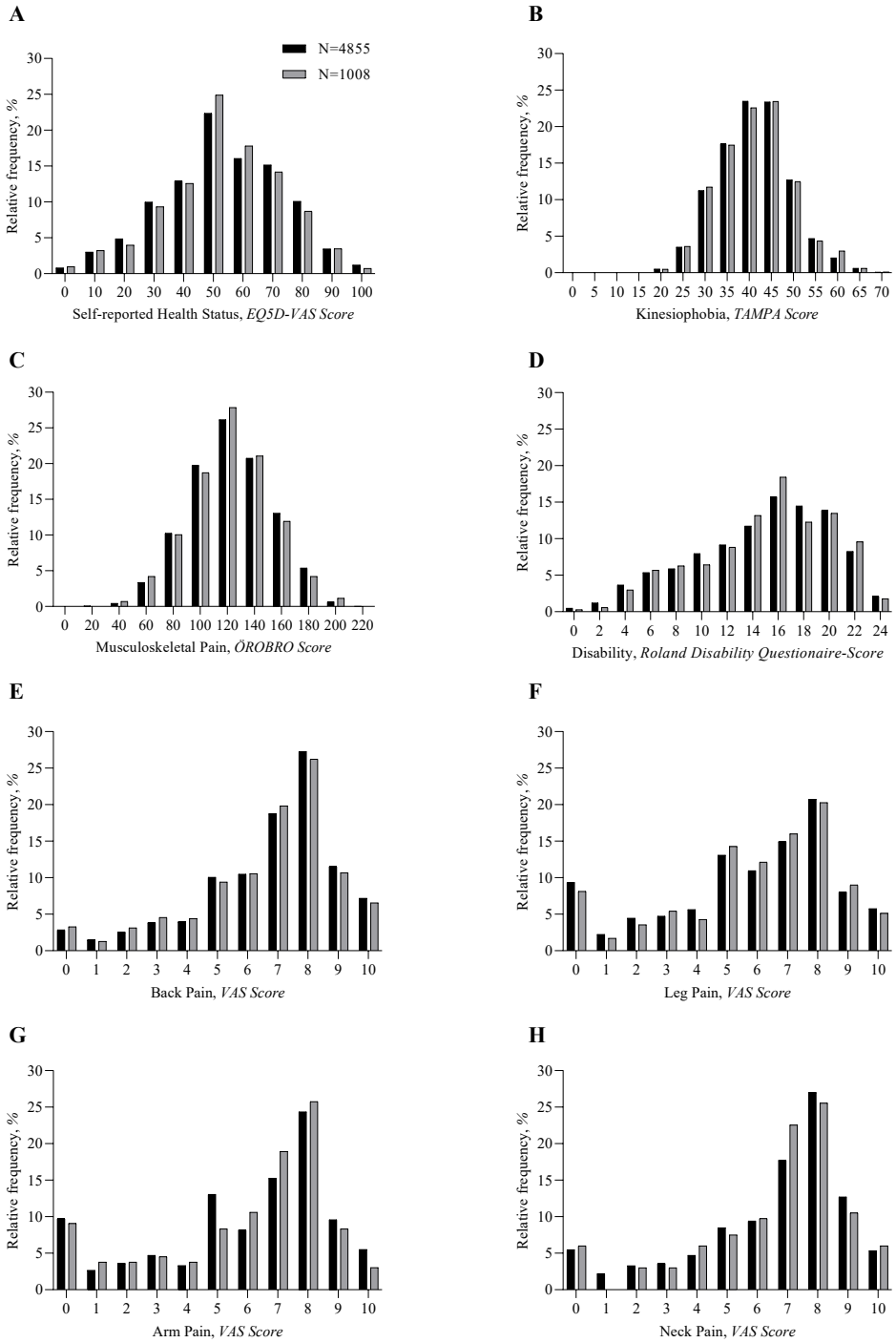

Figure 2.1A-H – Histograms of questionnaire scores.

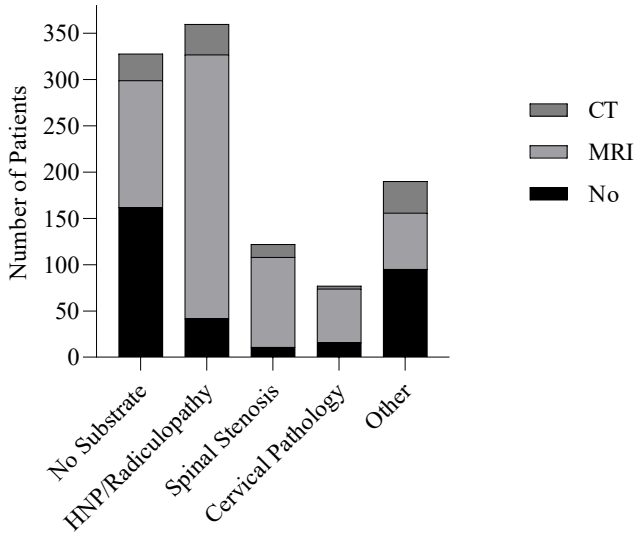

Figure 2. 2 - Imaging Diagnostics in Diagnosis-Groups.

3.5. Treatment

Non-surgical treatment was indicated for 959 patients (95%), and 49 patients (5%) were treated surgically (Table 2.4). Among all diagnosis groups, most patients received out-of-hospital treatment. In-hospital treatments consisted of treatment by a pain specialist (N=200, 20%), rehabilitation (N=67, 7%), referral to another specialist (N=26, 3%), and a corset (N=25, 2%). Out-of-hospital treatments consisted of physical therapy (N=441, 44%) and expectant management or referral back to general practitioner (N=353, 35%). Indicated treatment per diagnosis are visualized in Figure 2.3.

3.6. Additional diagnostics or in-hospital treatment

Of all 1008 patients, 238 patients (24%) received a second-opinion-only, without additional diagnostics or in-hospital treatment. Of these patients, the vast majority was diagnosed with spinal complaints without evident anatomical substrate (N=122, 51%), and 28 patients (12%) with a herniated nucleus pulposus or radiculopathy in the thoracolumbar region, 7 (3%) with spinal stenosis, and 11 (5%) with cervical pathology with neurological complaints. Seventy (29%) patients received other diagnoses. Of the 238 patients who did not receive additional diagnostics nor in-hospital treatment, 25-40% (~6-10% of all patients) had acceptable or good questionnaire scores, and considerably better scores on leg pain, arm pain and disability compared to patients that did receive in-hospital treatment or diagnostics. Histograms of the questionnaire scores comparing these groups are available in Appendix File 2.1.

Table 2.4 – Indicated treatment between diagnosis-groups.

	Spinal complaints without evident anatomical substrate (N=315)	HNP & radiculopathy thoracolumbar spine (N=332)	Spinal stenosis (N=110)	Cervical pathology with neurological complaints (N=75)	Other diagnoses (N=176)
Surgery	2 (0.6%)	17 (5%)	14 (13%)	2 (3%)	14 (8%)
Physical therapy	166 (53%)	144 (43%)	32 (29%)	31 (41%)	68 (39%)
Pain specialist	33 (10%)	97 (29%)	31 (28%)	19 (25%)	20 (11%)
Rehabilitation	33 (10%)	14 (4%)	5 (5%)	2 (3%)	13 (7%)
Expectant management	40 (13%)	77 (23%)	12 (11%)	28 (37%)	26 (15%)
General Practitioner	82 (26%)	32 (10%)	21 (19%)	3 (4%)	32 (18%)
Corset	13 (4%)	0 (0%)	5 (5%)	0 (0%)	7 (4%)
Referred to another specialist	9 (3%)	3 (1%)	4 (4%)	2 (3%)	8 (5%)
Other treatment	7 (2%)	13 (4%)	7 (6%)	4 (5%)	11 (6%)

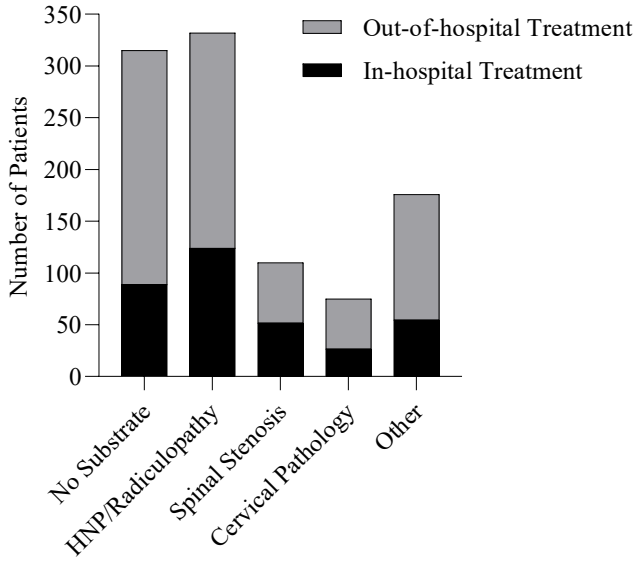

Figure 2. 3 - Treatments in diagnosis groups.

4. DISCUSSION

The objective of this study was to characterize the patient population at a Dutch, secondary spine center. In the Dutch health care system, access to specialized care requires referral by patients' general practitioner. Our study included all newly referred patients, resulting in a cohort that is representative for daily practice and comparable to other related studies[18,19]. Further we investigated the utilization of resources in the specialized health care center, namely additional diagnostics (MRI, CT), and specialized treatment, in addition to medical consultation by a specialist.

A substantial number of patients (70%) were overweight (BMI>25) or obese (BMI>30), which is 20% higher than the national average. Especially the proportion of patients with obesity is larger (30% in our cohort vs. 14% in the total population)[20]. This is representative of the results of a meta-analysis, which showed that overweight and obese patients were more likely to suffer low back pain, and had an increased tendency for seeking care[21]. This implies that preventive measures against overweight on the level of the population could have a direct impact on spinal care.

The disease burden in our population is supported by analgesic use and the reported symptoms of the referred population. In our study, we found that ~80% of patients reported using analgesics, of which around one-third used opioids, at the time of referral from primary care. These findings are in line with the findings of a disease-specific study performed by Ashworth et al., in which opioid prescription for low back pain in primary care was found to be 30%[22].

The impact of disease is also evident when comparing questionnaire scores about disability and quality of life to the healthy population or other serious diseases. For example, the mean self-reported health status, as assessed by EQ-5D VAS score on a scale to 100, was 53.3 among our study population, as compared to ~75 for an age-matched general population[11]. Scores were slightly worse in our population than scores of other study populations, for example patients suffering from chronic low back pain[23]. The mean VAS back pain score was 6.7, and was even higher in patients suffering from spinal complaints without evident anatomical substrate (7.3) of our cohort.

The high analgesics use and severe symptoms observed in our cohort strongly indicate the need for specialist care due to the high burden of disease for the population as such. A more detailed analysis reveals that despite the burden of disease, there is a significant proportion of patients, where the appropriateness of referrals remains unclear based on available data.

The vast majority of patients referred to the secondary spine center received non-surgical treatment, most often carried out outside of hospital, e.g., physical therapy, referral back to GP, or expectant management. Also, a quarter of all newly referred patients did not require specific in-hospital diagnostics or treatment. Importantly, the on average small differences and variability in characteristics and reported symptoms (by questionnaires) impede statistical patient-profiling for treatment selection with the available information. As of now, well-powered clinical research on the effects of non-surgical treatments for

the studied population is deficient. Insight in the effectiveness of such treatments for different diagnoses and subgroups of patients could drive forward our understanding of this complex category of patients, and ameliorate patient-selection for different types of treatments in primary and secondary healthcare.
Other studies have initiated revision of classic patient pathways and have generated promising results. One study investigated the efficacy of 'Primary Care Plus' for spine related complaints. In this study, patients that would normally be referred do secondary spinal care received multidisciplinary out-of-hospital consultation with standardized anamnesis, physical examination and diagnostics focused on red flags. Patients with suspected severe pathology were then referred to secondary care. Of all patients consulting Primary Care Plus, only ten percent required referral to secondary care. This was beneficial to patients, healthcare providers, and society in general, as it led to a significant reduction of time to diagnosis, while also reducing healthcare related costs[24].
A previously published study form Wilgenbusch et al. found that a coordinated pathway for referral of patients with low back pain resulted in over 50% more surgery candidates than the conventional referral process[25]. In our cohort, only 4.9% of patients were treated surgically. With the implementation of more strict pathways for referrals, the proportion of patients receiving in-hospital diagnostics and treatment might increase significantly. For these patients with severe symptoms with an identified anatomical substrate, as indicated by the necessity to treat surgically, questionnaire scores were indeed significantly worse than patients who were treated non-surgically.

4.1. Strengths and limitations

The main strength of this study is the size of the investigated cohort and the level of detail of data used. All data were collected prospectively, during the period of first outpatient visit after referral. This type of data-collection and retrospective analysis provides representative insight in the actual day-to-day healthcare, as opposed to prospective trials and randomized controlled trials.
This retrospective cohort study is limited by several constraints. The data used in this study are collected at the time of the first outpatient visit after referral. The missing data and the use of patient reported questionnaires could potentially lead to a selection bias[26]. Moreover, referral patterns and treatments strategies are region and healthcare-system specific, which may impact the generalizability of the study.
While our cohort consisted of a large sample size of nearly 5000 patients, the data regarding treatments, analgesics use and imaging diagnostics were manually extracted from the hospital records and is limited to the first 1008 patients of this cohort. We limited this detailed investigation due to the workload associated with this manual extraction, and thus these data do not necessarily reflect the outcomes of the entire cohort. However, based on demographics and questionnaires, the smaller cohort was comparable to the full cohort, and therefore likely representative. For future studies on more advanced patient profiling, even larger sample sizes are required, because

subgroups with less frequent indications are too small for considering covariates, e.g., demographic variables.

5. CONCLUSION

This retrospective cohort study provides insight in the characteristics of patients with spinal disorders referred to a secondary spine center. The burden of disease among these patients is high, and a large group of patients uses opioids to relieve their complaints. Only a select group of patients is treated surgically, whereas over 90% of patients is treated non-surgically. One-third of patients does not receive additional imaging diagnostics. The vast majority of conservatively treated patients received out-of-hospital treatment. Although we found several statistically significant differences in characteristics between groups of patients receiving different treatments, we found no variables that are sufficiently specific to aid in patient-profiling. Even though the outcomes of our study suggest that there is relevant potential for improvement of efficacy of referral, diagnosis and treatment, for example by triaging referrals, educating referring doctors, and organizing multidisciplinary out-of-hospital consultation, our lacking knowledge on the effectiveness of care pathways for different categories of patients impedes further healthcare optimization.

Large cohort trials or randomized controlled trials investigating the relationship between patient characteristics and effectiveness of new healthcare pathways including non-surgical treatments are mandatory to further develop healthcare allocation and conservative care for patients suffering from spinal complaints.

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APPENDIX FILE 2.1

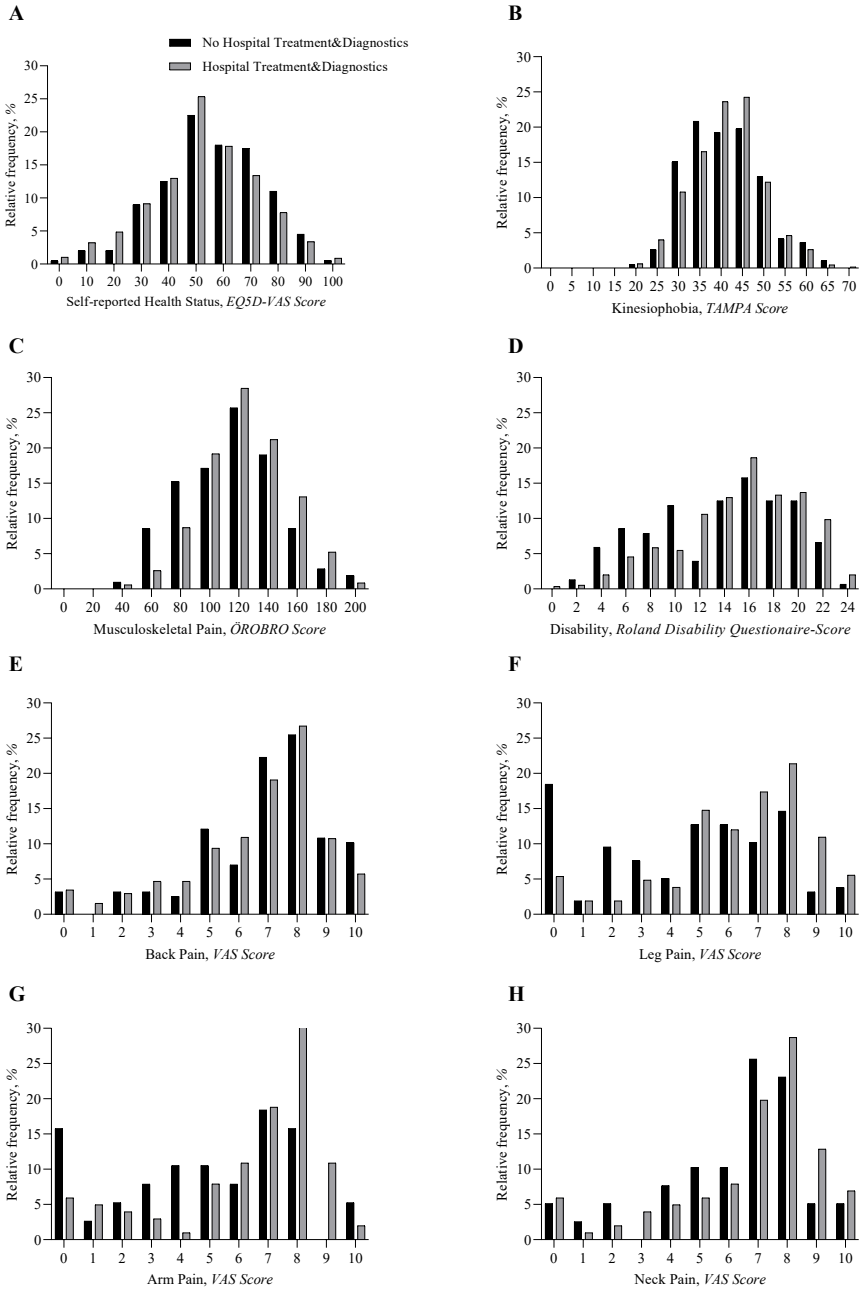
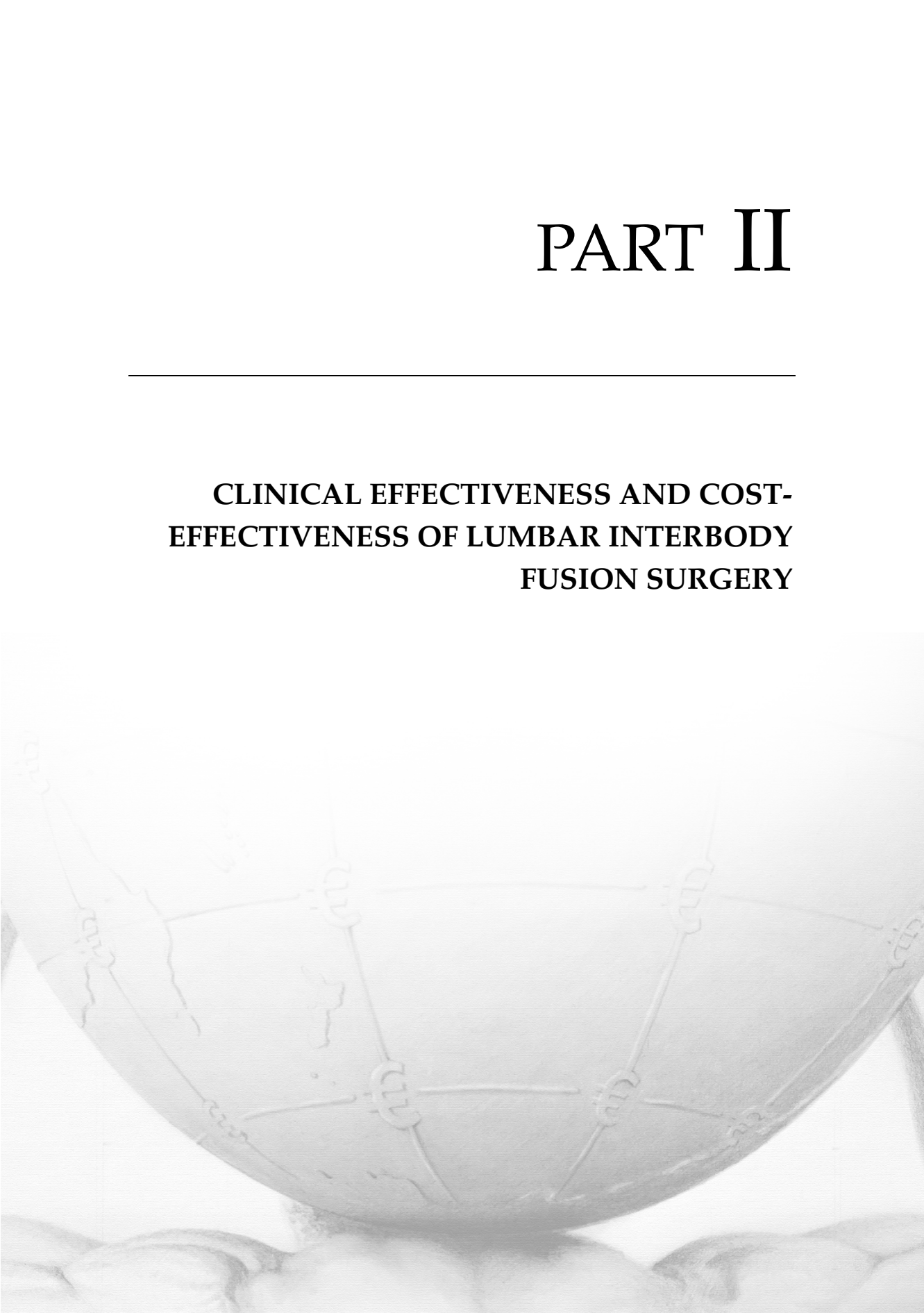


Figure S2.1 - Histograms of questionnaire scores, comparing patients receiving in-hospital care and no in-hospital care.

PART II

CLINICAL EFFECTIVENESS AND COST-EFFECTIVENESS OF LUMBAR INTERBODY FUSION SURGERY



CHAPTER 3

A RANDOMIZED CONTROLLED MULTICENTER TRIAL FOR SURGICAL TREATMENT OF LUMBAR SPONDYLOLITHESIS

The **L**umbar **I**nterbody **F**usion **T**rial (**LIFT)**

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*Both authors contributed equally to this work.

Submitted for publication.

ABSTRACT

Background
The effectiveness of transforaminal lumbar interbody fusion (TLIF) compared to posterior lumbar interbody fusion (PLIF) in patients with single-level spondylolisthesis has not been substantiated. To address the evidence gap, a well-powered randomized controlled non-inferiority trial comparing the effectiveness of TLIF with PLIF, entitled the Lumbar Interbody Fusion Trial (LIFT), was conducted.

Methods
In a multicenter randomized controlled non-inferiority trial among five Dutch hospitals, 161 patients were randomly allocated to either TLIF or PLIF (1:1), stratified according to study site. All patients were over 18 years old with symptomatic single-level degenerative, isthmic or iatrogenic lumbar spondylolisthesis, and eligible for lumbar interbody fusion surgery through a posterior approach. The primary outcome was change in disability measured with the Oswestry Disability Index (ODI) from preoperative to one year postoperative. Secondary outcomes were change in quality-adjusted life years (QALY) assessed with EuroQol 5 Dimensions, 5 Levels (EQ-5D-5L) and Short Form Health Survey (SF-36), as well as back and leg pain (Visual Analogue Scale; VAS), anxiety and depression (Hospital Anxiety Depression Scale; HADS), perioperative blood loss, duration of surgery, duration of hospitalization, and complications.

Results
Per-protocol analysis included 66 patients in each group. In the TLIF group, ODI improved from 46.7 to 20.7, whereas in the PLIF group, it improved from 46.0 to 24.9. This difference did not reach statistical significance over time ($P=0.28$). A significant but not clinically relevant difference in QALY (SF-36) was observed in favor of TLIF ($P<0.05$). For all other PROMs, (ODI, EQ-5D, VAS leg/back, HADS), a non-significant difference was observed twelve months postoperatively. There was no difference in perioperative blood loss, duration of surgery, duration of hospitalization, and perioperative or postoperative complications between TLIF and PLIF.

Conclusion
For patients with single-level spondylolisthesis, TLIF is non-inferior to PLIF in terms of clinical effectiveness. Disability (measured with ODI) did not differ over time between groups. TLIF showed a significant difference in change over time in QALY compared to PLIF measured with SF-36, which was not clinically relevant.

1. INTRODUCTION

Lumbar spondylolisthesis with subsequent central or foraminal stenosis is a common cause of neurogenic leg pain[1]. The incidence of symptomatic spondylolisthesis increases with age due to spinal degeneration. Spine disorders are responsible for the highest burden of disease in terms of years lived with disability (YLD), and in this perspective, contributes to disability more than cancer, cardiovascular diseases, or mental disorders[1].
For patients with symptomatic spinal stenosis, surgical treatment in most cases is inevitable. As the incidence continues to rise, the need for lumbar fusion surgery also increases[2-8].
When decompression and fusion is indicated, transforaminal lumbar interbody fusion (TLIF) and posterior lumbar interbody fusion (PLIF) are commonly used. Both procedures include pedicle screw placement and intervertebral cage insertion. In the TLIF procedure, this is achieved by placement of one cage in the intervertebral space, using a unilateral transforaminal approach. The PLIF procedure involves placing two identical cages bilaterally in the intervertebral space, using a bilateral central approach.
Specific indication for the use of either technique is unknown, therefore the choice of technique is frequently based on the surgeon's preference. Although these techniques are assumed to be equally effective, nonrandomized studies and one small randomized controlled trial (RCT) comparing TLIF and PLIF suggest that TLIF is associated with fewer complications, less blood loss, and shorter length of surgical procedure and hospital stay[9-12]. It is evident that there is a need for high-quality comparative data to develop evidence-based treatment recommendations. Therefore, a well-powered non-inferiority randomized controlled trial comparing the effectiveness of TLIF and PLIF in patients with single-level lumbar spondylolisthesis, entitled the Lumbar Interbody Fusion Trial (LIFT), was conducted.

2. METHODS

2.1. Trial design

A multicenter randomized controlled non-inferiority trial was conducted. Patients were randomly assigned in a 1:1 ratio to undergo either TLIF or PLIF. This study was approved by the local institutional medical ethical committee (Medical Research Ethics Committee Zuyderland, METC 16-T-36) and previously registered within the International Clinical Trials Registry Platform (ICTRP, Main ID NTR5722).

2.2. Study population

Patients were included from five Dutch hospitals between August 2017 and November 2020. Inclusion and exclusion criteria of patients are listed in Table 1. When eligible to participate, informed consent was acquired.

Table 3.1 - Inclusion and exclusion criteria of LIFT-study.

Inclusion criteria	Exclusion criteria
Indication for LIF through posterior approach	Previous radiotherapy at the intended surgical level
Clinical single level, uni- or bilateral, lumbar radiculopathy or intermittent neurogenic claudication	(progressive) Motor failure and/or anal sphincter disorders which urges instant intervention
Single level isthmic, degenerative or iatrogenic spondylolisthesis	Active infection
Spondylolisthesis Meyerding classification grade I, II or III	Immature bone (ongoing growth)
Spondylolisthesis at level L3L4, L4L5 or L5S1	Active malignancy
Central or foraminal stenosis on MRI (or CT) of which the anatomical level is corresponding to the clinical syndrome	Pregnancy
Age over 18 years	Symptomatic osteoporosis (defined on DEXA-scan or the use of bisphosphonates)
Psychosocially, mentally, and physically able to fully comply with this study protocol	Contra-indications for anesthesia or surgery
	Inadequate command of the Dutch language

Abbreviations: LIF= lumbar interbody fusion, DEXA= Dual Energy X-ray Absorptiometry.

Patients were excluded from the one-year effectiveness analyses if loss to follow-up occurred before completion of the one-year questionnaires.

2.3. Randomization and blinding

Patients were randomized into one of two parallel groups (1) TLIF and (2) PLIF in a 1:1 ratio, using web-based computer-generated block randomization with sizes of 4, 6, 8, stratified by designated hospital. The outcome of randomization was revealed to the surgeons preoperatively. Patients were blinded during the entire follow-up period. The statistician performing the final analyses was blinded as well.

2.4. Outcome measurements

The primary outcome measurement was change in disability, measured with the Oswestry Disability Index (ODI). Secondary outcome measurements were quality-adjusted life years (QALY) assessed with EuroQol 5 Dimensions, 5 Levels (EQ-5D-5L) and Short Form 36 Health Survey (SF-36), pain assessed with the Visual Analogue Scale (VAS) score for back pain and leg pain, and presence of anxiety or depression assessed with Hospital Anxiety Depression Scale (HADS). All patients were asked to complete patient reported outcome measurements (PROMs) questionnaires (web-based or on

paper) preoperatively and at three, six and twelve months postoperatively. Questionnaires were unrelated to any hospital visit, and were completed without assistance of medical personnel or any other professionals involved in the trial.
Per PROM, the difference between preoperative and twelve months postoperative was compared with the minimal clinically important difference (MCID). For ODI, this MCID was set across 7.0 points[13]. For HADS, scores above 11 were patients with 'probable anxiety and depression', scores between 8 and 11 were patients with 'possible anxiety and depression' and scores below 8 were patients with 'no anxiety and depression'[14]. MCID of HADS is set across 1.5 points[15], and MCID of SF-36 ranged from 3.0 to 5.0 points[16]. MCID of EQ-5D was set at 0.31[13], and MCID of VAS back and VAS leg were set at 3.0 and 2.0 points, respectively[13].
Perioperative morbidity was determined based on intraoperative blood loss, duration of surgery, and duration of hospitalization. Direct and indirect surgical complications, including dural tears, postoperative infection, deep venous thrombosis, hematoma, hardware failure, neurological deficits, and other complications such as pneumonia or urinary tract infection were collected.

2.5. Interventions

2.5.1. General

Antibiotic prophylaxis according to local hospital protocol was administered. Subsequently, the patient was brought under general anesthesia and positioned prone. After preparing, disinfection and draping, a midline posterior approach was performed, exposing the posterior lumbar elements including facet joints. Poly-axial pedicle screws were inserted bilaterally, using fluoroscopic guidance or navigation, based on the surgeons' preference. In case of central spinal canal stenosis, a laminectomy was performed to decompress the neural structures. In both approaches, a titanium rod interconnected the screws on each side. The wound was thoroughly irrigated and closed in several layers without suction drainage.
Either TLIF or PLIF was subsequently performed according to randomization.

2.5.2. TLIF

Unilateral exposure to the intervertebral disc was achieved by total unilateral facetectomy, decompressing the descending, and leaving roots. In case of bilateral symptomatic leg pain, the side of the unilateral approach was based on the most symptomatic side; in case of equal distribution, it was based on the surgeons' preference. Unilateral facetectomy was performed to gain access to the intervertebral disc. Discectomy was performed. Endplate cartilage was prepared to provide a host bed of bleeding subchondral bone for placement of the cage. The TLIF cage size was determined by a trial cage under fluoroscopic guidance. The definitive cage was packed with autologous bone or allograft, and tamped into place. Its position was checked

radiologically. After placement of the TLIF cage, the remainder of the disc space was filled with autologous bone obtained from the laminectomy.

2.5.3. PLIF

Bilateral access to the intervertebral disc was assured by medial facetectomy. Bilateral discectomy was performed. Subsequently, endplate cartilage was prepared to provide a host bed of bleeding subchondral bone for placement of the cages. The size of the PLIF cages was determined by a trial cage under fluoroscopic guidance. Before placement of the definitive cages, the disc space was partially filled with autologous bone, obtained from decompression. The definitive cages were also packed with autologous bone or allograft, and tamped into place. Their position was checked radiologically.

2.5.4. Postoperative care

Patients were encouraged to mobilize, initially with guidance of a physiotherapist, and to resume daily activities as soon as possible. No additional physical therapy was routinely advised. Patients were administered postoperative pain medication according to the local hospital protocol.

2.6. Sample size

Change in ODI, defined as the difference between preoperative and postoperative ODI, was the primary endpoint and used for calculating the sample size. Assuming that there were no differences in the change in ODI after one year, the non-inferiority limit was set to 7.0 points based on the MCID. Based on our own retrospective data set, the response data from the ODI within each subject group was normally distributed, with standard deviation of 16[17]. This resulted in a total of 64 experimental subjects and 64 control subjects needed to be able to reject the null hypothesis that TLIF is inferior to PLIF with probability (power) of 0.8. The Type I error probability associated with this test of this null hypothesis is 0.05.
A loss-to-follow-up rate of 10% was initially accounted for. However, long waiting times for surgery during the COVID-19 pandemic resulted in patients seeking care elsewhere, hence drop-out was higher than anticipated and accordingly adjusted to 20%. When accounting for a 20% loss-to-follow-up, 160 patients (80 patients per group) needed to be enrolled in this study. As inclusion occurred simultaneously in the participating centers, a total of 161 patients were included.

2.7. Statistical analyses

Clinical effectiveness data were analyzed according to the per-protocol principle. Differences in PROMs between baseline and the twelve-month follow-up were analyzed using generalized linear mixed models (for non-normally distributed baseline data), with time, type of surgery and time*type of surgery interaction as fixed factors. Baseline and

surgical characteristics were compared between groups using Student's T-test, Median Tests or Chi-Square tests for continuous, normally distributed data, for continuous, non-parametric data or categorical data, respectively. All results were presented as absolute mean differences with 95% confidence intervals (CI), or odds ratios with 95% CI. The level of significance was set at $P<0.05$.

3. RESULTS

3.1. Study population

The total study population of the LIFT study was 161 patients. Total loss-to-follow-up after one year was 16 patients. Of these, ten had refrained from filling out postoperative PROMs without a specific reason, three withdrew from the study before randomization, two died because of unrelated causes, and one patient developed severe cognitive impairment. Thirteen patients required different surgery than the outcome of the dictated randomization process. In five of these patients, cage insertion was impossible; four patients required multi-level surgery, two underwent minimally invasive TLIF, one PLIF-group patient underwent a TLIF, and one TLIF patient underwent a PLIF. In total, 132 patients were included in the per-protocol analyses, of which 66 patients received TLIF and 66 patients received PLIF (Figure 3.1). Patients' characteristics are described in Table 3.2. In the PLIF group, significantly more patients were diagnosed with diabetes.

3.2. Primary outcome

The primary outcome – disability measured with ODI – improved significantly over time after lumbar interbody fusion in both the TLIF and PLIF group. The difference in change over time between groups did not reach statistical significance ($P=0.28$). Both groups improved more than 14.0 points in ODI after one year. For TLIF, the ODI changed from 46.7 preoperatively to 20.7 at twelve months after surgery, while for PLIF the ODI changed from 46.0 to 24.9. Changes in ODI score over time are visualized in Figure 3.2A.

3.3. Secondary outcome

All secondary outcomes improved significantly over time after surgery for both groups. A significant difference in change over time in QALY, measured with SF-36, was observed in favor of TLIF compared to PLIF ($P<0.05$). For all other PROMs, (EQ-5D-5L, VAS back and leg, HADS), a non-significant difference was observed twelve months postoperatively (Figure 3.2B-G).
Surgical characteristics are described in Table 3.3. There were no significant differences in intraoperative blood loss, duration of surgery, duration of hospitalization, and occurrence of dural tears or complications during hospitalization.

Within one year, 12 complications occurred. Five complications were hardware related; pedicle screw malposition (n=2, TLIF), pedicle screw breakage (n=1, PLIF), and rod extrusion (n=1, TLIF). Reoperation was required for four of these. Furthermore, there was one patient with asymptomatic screw migration (n=1, TLIF). In both groups, two patients developed adjacent segment disease, one of which in the TLIF group required extension of the fusion. In the PLIF group, one patient suffered an atraumatic fracture of the vertebral body, which required extension of the spinal construct. In the TLIF group, two patients developed wound infection early after hospital discharge.

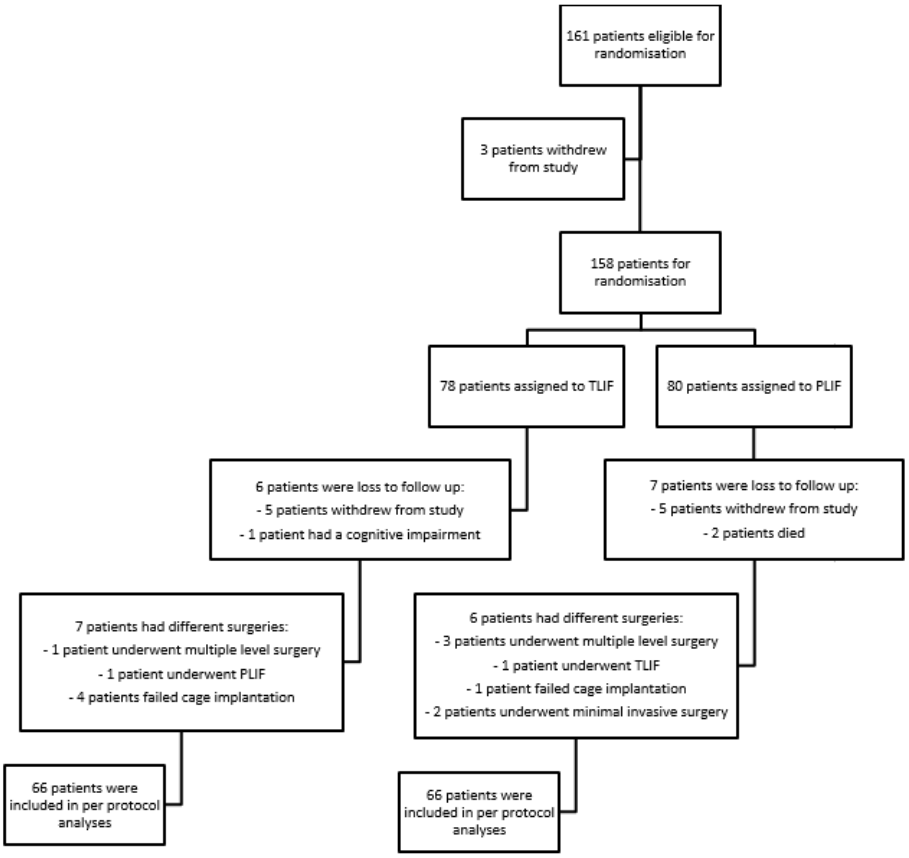

Figure 3.1 - Flowchart of study population of the LIFT-study.

Table 3.2. - Baseline characteristics of included patients divided between TLIF and PLIF group. P-value<0.5 stands for statistically significant difference, which is marked with *.

Variable	TLIF (N=66)	PLIF (N=66)	P-value	95% Confidence Interval of the difference	
				Lower	Upper
Age in years, mean (SD)	61.6 (12.0)	61.9 (9.7)	0.85	-4.1	3.4
Sex, (% (N) female)	54.5% (36)	62.1% (41)	0.38	-	-
BMI, mean (SD) $kg.m^{-2}$	27.7 (4.7)	27.6 (5.1)	0.91	-1.6	1.8
Diabetes (% (N) yes)	4.5% (3)	15.7% (10)	0.03*	-	-
Smoking status (% (N) yes)	25.8% (17)	18.2% (12)	0.29	-	-
Number of Pack years, mean (SD)	25.0 (17.9)	26.6 (17.1)	0.78	-13.0	9.9
Mean duration of complaints in months, median	17	16			
Indication of surgery (% (N) yes)					
Degenerative spondylolisthesis	59.1% (39)	75.8% (50)	0.09	-	-
Iatrogenic spondylolisthesis	6.1% (4)	1.5% (1)	-	-	-
Lytic spondylolisthesis	34.8% (23)	22.7% (15)	-	-	-
Grade of spondylolisthesis (% (N) yes)					
I	80.3% (53)	83.3% (55)	0.65	-	-
II	19.7% (13)	16.7% (11)	-	-	-
ASA classification (% (N) yes)					
I	7.6% (5)	15.2% (10)	0.08	-	-
II	81.8% (54)	60.6% (40)	-	-	-
III	10.6% (7)	24.2% (16)	-	-	-
Level of surgery (% (N) yes)					
L3L4	7.6% (5)	9.1% (6)	0.27	-	-
L4L5	62.1% (41)	72.7% (48)	-	-	-
L5S1	30.3% (20)	18.2% (12)	-	-	-

Abbreviation: TLIF= Transforaminal Lumbar Interbody Fusion, PLIF= Posterior Lumbar Interbody Fusion, SD= Standard Deviation, BMI= Body Mass Index, ASA classification= American Society of Anesthesiologists classification.

Table 3.3 - Surgical characteristics of included patients divided between TLIF and PLIF group. P-value<0.5 stands for statistically significant difference, which is marked with *.

Variable	TLIF (N=66)	PLIF (N=66)	P-value	95% Confidence Interval of the difference	
				Lower	Upper
Duration of surgery in minutes, mean (SD)	153.0 (44.6)	158.4 (40.8)	0.47	-20.1	9.3
Blood loss in cc, mean (SD)	348.1 (197.5)	357.2 (198.6)	0.79	-77.9	59.6
Dural tear (% (N) yes)	7.6% (5)	10.6% (7)	0.55	-	-
Duration of hospitalization in days, mean (SD)	4.8 (4.8)	4.9 (5.0)	0.85	-1.8	1.5
Complications during hospitalization (% (N) yes)	21.1% (14)	22.7% (15)	0.83	-	-
Wound infection	1.5% (1)	0	-	-	-
Hematoma	6.1% (4)	4.5% (3)	-	-	-
Neurological complaints	4.5% (3)	3.0% (2)	-	-	-
Other complications (e.g., UTI, pneumonia)	9.1% (6)	18.2% (12)	-	-	-

Abbreviation: TLIF= Transforaminal Lumbar Interbody Fusion, PLIF= Posterior Lumbar Interbody Fusion, SD= Standard Deviation, UTI= Urinary Tract Infection.

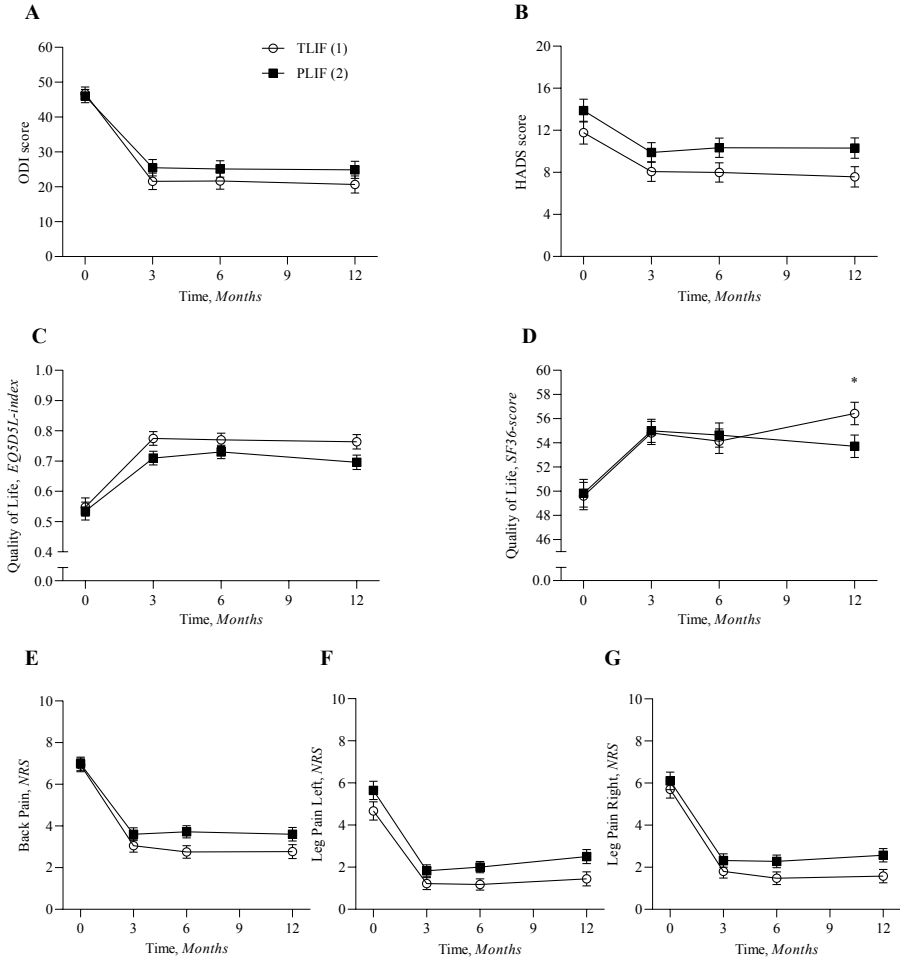

Figure 3.2 - PROMs at baseline, and three, six and twelve months postoperatively of included patients divided between TLIF and PLIF.

3.4. Intention-to-treat analysis

The intention-to-treat analysis, which compared the characteristics and available outcomes of the included (N=132) and excluded (N=29) patients in the per-protocol analysis, yielded similar outcomes as the per-protocol analysis.

4. DISCUSSION

The LIFT is the first well-powered randomized controlled non-inferiority trial to determine effectiveness of TLIF and PLIF in patients with single-level lumbar spondylolisthesis. The most important finding of this study is that TLIF is noninferior to PLIF. Both procedures are equally effective in reducing disability (ODI), as they both reached the pre-defined MCID of 7.0.
Secondary outcome measurements showed that quality of life (EQ-5D-5L), back and leg pain (VAS), and anxiety and depression (HADS) did not differ between TLIF and PLIF groups. Clinically relevant differences based on previously reported MCID was reached for both TLIF and PLIF for HADS (>1.5 points), VAS back and leg (>3 points) and SF-36 (>3 points). EQ-5D was the only MCID that was not reached after TLIF or PLIF surgery, as the difference was only 0.31 points. However, a previous systematic review by Coretti et al. determined a broad MCID range used for EQ-5D in the clinical area of musculoskeletal disorders; MCID was 0.03 in a study of patients with low back pain, while it was 0.52 in a study of patients with recurrent lumbar stenosis[18]. This suggests that there is no consensus for which disease-specific MCID to use in EQ-5D outcomes. The significant difference in quality of life (SF-36) in favor of TLIF did not exceed the MCID.
Furthermore, results showed that both interventions are comparably safe, as reflected by the amount of intraoperative blood loss, duration of surgery, duration of hospitalization, and complications rate.

The results of this study are similar to a previously published systematic review with meta-analyses, which described comparable results in ODI for PLIF and TLIF[9]. This was also suggested in a low-powered study that described no significant difference in ODI[10].
In our study, a significant difference in change over time in quality of life (SF-36) was observed in favor of the TLIF. Subdomains of the SF-36 and EQ-5D were assessed to evaluate if this difference was driven by large differences in a specific domain. However, subdomains of SF-36 and EQ-5D were similar. In a previous analysis by McDonough et al. comparing the SF-36 and EQ-5D, it was apparent that outcomes of quality of life cannot be compared accurately between both scores among spine patients[19].
Although, the difference between TLIF and PLIF for other outcome measures did not reach statistical significance, it is remarkable that all studied PROMs still showed a difference over time in favor of the TLIF. It is uncertain whether these small differences are the result of coincidences, or whether outcome parameters are not sensitive enough to detect existing differences. It can be postulated that the success of the surgery is defined by adequate decompression instead of the superiority of one technique over another, as both techniques have the same objective: decompression of the nerve roots and stabilization of the spine. Indeed, the hypothesized slightly better primary and secondary outcomes were in favor of TLIF, because of less extensive iatrogenic damage during

surgery, possibly resulting in less fibrous tissue over time. However, these were deemed to be clinically irrelevant.
On the contrary, it is suggested that unilateral decompression and cage insertion could result in less iatrogenic radiculopathy or dysfunction, and dural tears[9,20]. The small difference in occurrence of dural tears in our study might be explained by the unilateral decompression in TLIF opposed to bilateral in PLIF. However, as this was not significant, it was ruled out as a major decisive factor.
It is notable that there were no significant differences in intraoperative blood loss, or duration of surgery or hospitalization. Duration of surgery was evaluated in several previous trials and reviews. No differences were described in the systematic review of Teng et al.[20], while in the RCT of Yang et al., duration of surgery was 113 minutes for TLIF and 125 minutes for PLIF, resulting in a significant difference with a P-value below 0.05[10]. Although we believe that a difference of 12 minutes is not clinically relevant, it could nevertheless be relevant in the cost-effectiveness analysis. In LIFT, it is possible that surgeons might have chosen a broader decompression in patients with lumbar spinal stenosis undergoing TLIF, which could have reduced the advantage in duration of surgery of the unilateral TLIF approach. Insertion of two cages in PLIF (instead of one cage in TLIF) might explain the non-clinically relevant difference of five minutes between groups. The similarity in blood loss and duration of hospitalization could be explained by using a midline approach in both groups, which resulted in less difference in muscle dissection and therefore muscle recovery. Another reason for comparable duration of hospitalization is the use of standardized rehabilitation.

4.1. Strengths and limitations

This is the first well-powered randomized controlled trial that compares effectiveness of TLIF and PLIF in patients with lumbar spondylolisthesis. The methodological implementation of this study was of high quality due to its multicenter nature, the number of loss-to-follow-up remaining within the range of the pre-calculated 20%, adequate randomization, and blinding of patients and the statistician to minimize bias. To reach the aim of our study, which was primarily to compare disability of PLIF and TLIF, a per-protocol analysis was performed.
The study could be influenced by possible limitations. The study protocol described a detailed surgical approach for both TLIF and PLIF[21]. Nevertheless, it is possible that surgeons determined that more bony decompression was needed during surgery, mostly in the case of TLIF patients, if the surgeons believed indirect decompression of the contralateral neuroforamen would not be sufficient. This could have led to a less unilateral approach with laminectomy, resulting in a smaller difference between TLIF and PLIF in surgical variables. TLIF procedures can be performed using less invasive approaches. For example, the paramedian approach with percutaneous screw fixation on the contralateral side, potentially leading to less paravertebral muscle dissection, compared to the midline approach without percutaneous screw fixation. For reasons of blinding of participants in this study, a paramedian approach was not investigated.

Furthermore, it is possible that the results are skewed because of a disproportional dominance in inclusions of one of the participating centers.

4.2. Future recommendations

The number of lumbar fusion surgeries has increased rapidly in the past decade[22]. Moreover, this number will continue to rise, since an aging population is correlated with degenerative diseases of the spine[23]. This rising number also means higher healthcare costs for lumbar fusion surgery[24,25]. Due to the lack of high-quality studies, surgeons greatly base their choice of surgical method on experience and preference, instead of scientific evidence on effectiveness and cost-effectiveness. Recent reviews could not fill this knowledge gap due to low-quality of included studies and heterogeneity in the reported results[9,12]. The 12-month results of the LIFT, which is a high-quality randomized controlled trial, fills this knowledge gap on effectiveness. Recently, a newer minimally invasive variation of TLIF has started gaining popularity; the minimally invasive transforaminal lumbar interbody fusion (MI-TLIF). In this approach, decompression and cage insertion are performed through tubular retractors, followed by percutaneous posterior pedicle screw fixation[26]. Previous literature described varying results on the clinical superiority of MI-TLIF over TLIF. However, there are no proper comparisons between MI-TLIF and the most favorable open technique. After final analyses of the LIFT, the most favorable open lumbar interbody fusion surgery technique, based on effectiveness and cost-effectiveness, should be compared with MI-TLIF.

5. CONCLUSION

This multicenter randomized controlled trial proved that TLIF is non-inferior to PLIF regarding clinical effectiveness. Potential future differences in cost-effectiveness between TLIF and PLIF may be a decisive factor for employing either technique. Until then, it will remain left to the surgeons' preference.

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CHAPTER 4

PROCESS EVALUATION OF LUMBAR INTERBODY FUSION SURGERIES IN FIVE DUTCH HOSPITALS, A QUALITATIVE ANALYSIS

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ABSTRACT

Background and objectives
Only limited qualitative research concerning instrumented spine surgeries has been published, despite the increasing number of these surgeries and the evident importance of qualitative analysis of the processes surrounding these complex interventions. Current qualitative research is mainly limited to the experiences, emotions and expectations of patients. Insight in the full process, including experiences from the perspective of informal caregivers and healthcare professionals remains scarce.

Materials and methods
Data were gathered by means of semi-structured face-to-face interviews. In total, 27 participants were included, of which 11 patients, 7 informal caregivers and 9 healthcare professionals. A semi-structured interview guide was used. The interview process was audiotaped and each interview was transcribed verbatim. To systematically analyze the gathered data, software for qualitative analysis (NVivo) was used. After immersion in the raw data of transcripts and field notes, a list of broad categories for organizing the data into meaningful clusters for analysis, was developed. Subcategories were created for each main category, which were elaborated and complemented during the data analysis. All interviews were coded by the first author and 25% was independently assessed by the second author. In author meetings between the first and second author, the categories, subcategories and coding were discussed and consensus was reached.

Results
The results of our study describe several promoting and limiting factors concerning the process of lumbar fusion surgery, from the perspective of patients, informal caregivers and healthcare providers. The most frequently mentioned promoting factors were; information and opportunities to ask questions during consultations, multidisciplinary consultations, good communication and guidance during hospitalization, and follow-up appointments. The most frequently mentioned limiting factors were; lack of educational material, lack of guidance and communication prior to, during, and after hospitalization.

Conclusion
Overall, participants were satisfied with the current healthcare-process in lumbar fusion surgery. However, we found that lack of educational material and guidance during the process led to insecurity about complaints, surgery, and recovery. To improve the process of lumbar interbody fusion and to increase patient satisfaction, healthcare providers should focus on guiding and educating patients and informal caregivers about the pre-operative trajectory, the surgery, and the recovery. From the healthcare providers perspective, the process could be improved by multidisciplinary consultations and a dedicated spine team in the operation room. Although this study focusses on lumbar fusion surgery, results could be translated to other fields of spine surgery and surgery in general.

1. INTRODUCTION

Since 1980, the global population of people older than 60 years has doubled. This number is expected to double again by 2050[1]. Ageing of the population is one of the most prominent factors by which the number of instrumented spine surgeries has increased and will increase even further in the future[2,3]. Therefore, it is of significant importance to analyze, evaluate, and eventually optimize the efficiency of the healthcare-process and patient satisfaction[4].

Despite the increasing number of instrumented spine surgeries and the evident importance of qualitative analysis of the processes surrounding complex interventions, only limited qualitative research has been published concerning this subject. Current qualitative research is mainly limited to the experiences, emotions and expectations of patients. Insight in the full process, including experiences from the perspective of informal caregivers (ICG) and healthcare professionals remains scarce[5-8].

The aim of this study was to gain insight in the full process surrounding lumbar fusion surgery in five Dutch hospitals. Steps in the process were evaluated by patients, informal caregivers and healthcare professionals. The ultimate goal of the study was to provide insightful qualitative data that can be used to optimize the healthcare process of lumbar interbody fusion surgeries.

2. MATERIALS AND METHODS

The qualitative analysis described in this article is part of a large randomized controlled trial on the effectiveness and cost-effectiveness of transforaminal lumbar interbody fusion (TLIF) compared to posterior lumbar interbody fusion (PLIF); the LIFT-study. The results of this study will be published elsewhere. Ethical approval was granted and all participants provided signed informed consent before participating in the study. (LIFT-study. NTR5722; Dutch Trial Register. NL54717.096.16; CCMO.)

2.1 Recruitment and sample size

In total, 27 participants from five different hospitals were included, of which 11 patients, seven informal caregivers and nine healthcare professionals (three orthopedic surgeons, three neurosurgeons two specialized nurses and one physician assistant).

Patients scheduled for lumbar interbody fusion surgery, their informal caregivers, specialized nurses, nurse consultants, neurosurgeons and orthopedic surgeons were recruited to participate in this study. These groups were selected based on their unique experiences during participation in the healthcare process of fusion surgery. Patients undergoing TLIF or PLIF were recruited for the LIFT-study in five participating hospitals in the Netherlands by two researchers (RD and IC). Eligible patients were over 18 years of age and had good comprehension of verbal and written Dutch. Informal caregivers of

participating patients were likewise recruited. After informed consent, patients and informal caregivers were randomly selected for an interview. The principal investigators of the LIFT-study from each participating hospital were interviewed (Zuyderland Medical Center Heerlen, Maastricht University Medical Center +, Canisius Wilhelmina Ziekenhuis, VieCuri Medical Center, University Medical Center Groningen). Furthermore, when fusion surgeries were performed by a neurosurgeon and orthopedic surgeon, both specialists were interviewed. This was the case in two hospitals. If applicable, specialized nurses, nurse consultants or physician assistants specialized in spine surgeries were likewise participated in this study. All healthcare providers gave written informed consent to participate in this study.
Inclusion started in 2017 and was completed in 2020. Inclusion stopped when both researchers agreed on the fact that the new interviews did not lead to new information or insight, only adding new instances of already existing themes, without adding new ones (i.e., the point of saturation) and the included cohort had reached maximum variation with regard to the hospital where surgery was performed[9].

2.2. Data collection

Data were gathered by means of semi-structured face-to-face interviews. The interviews with the patients and informal caregivers took place three months after surgery, as it was expected that patients had recovered to the extent that they could resume daily activities, including self-care. Furthermore, it was expected that the patients could reflect on the entire process, without forgetting essential information. All the participants were interviewed by the same researcher (IC). They could choose whether they felt more comfortable to be interviewed either in their homes, or in the privacy of a consulting room within the hospital premises. During the COVID-19 pandemic, participants were interviewed through videoconferencing. The interviewer (IC) was not involved in the treatment of the patients. A semi-structured interview guide, developed prior to the start of the study, was used (Appendix File 4.1). These questions were based on participant observation, with researchers attending and observing the process during outpatients' clinics and hospital admission. Researchers obtained additional information from healthcare professionals working in this area. Open-ended questions were included to establish a general direction for the interview. The experiences of the participants were further elaborated upon by follow-up questions. The median duration of the interviews was 34 minutes (range 12-78). The interview process was audiotaped, and each interview was transcribed verbatim by RD and IC. To further increase credibility, all participants received transcripts of their interviews and were given the opportunity to provide feedback or additional information.

2.3. Data analysis

To systematically analyze the gathered data, the NVivo Version 1.3 software for qualitative analysis was used[10]. After immersion in the raw data of transcripts and field

notes, a list of broad categories (codes in NVivo), for organizing the data into meaningful clusters for analysis, was developed. To evaluate the process in a comprehensible fashion, the process was categorized as "pre-hospitalization", "peri-hospitalization" and "post-hospitalization". A detailed description of the full process is provided below. For data-analysis, an iterative approached was used. At the start of data-analysis, categories and subcategories were created based on the interview guide and the interviewers experience. During data-analysis, these categories were evaluated, adjusted and complemented by two authors (RD and IC) continuously throughout the process. The final list of codes is presented in Appendix File 4.2. All interviews were coded by the first author (RD). To increase objectivity, the second author (IC) went through 25% of the transcripts and independently assessed the coded data from the interviews according to the list of categories produced by the first author. In author meetings between the first and second author, the categories, subcategories and coding were discussed and consensus was formed on how data was categorized. As all interviews were conducted in Dutch, the interview guides and reported citations were translated into English.

2.4. Process description open lumbar interbody fusion surgeries

The process as described below is in accordance with the protocol of the randomized controlled trial on which this qualitative study is based. This description is based on participant observation in two participating hospitals. Furthermore, orthopedic surgeons and neurosurgeons of the other three participating hospitals were asked about the regular process of lumbar fusion surgeries in their hospital. The processes of the participating hospitals were compared and combined to one uniform process description by one of the authors (IC). Before start of the interviews, all principal investigators verified the process description.

2.4.1. Pre-hospitalization

Patients with lower back pain and radiculopathy or neurogenic claudication are referred to the hospital by the general practitioners (GP). Depending on the GP's referral, the patient is examined by either a neurologist or orthopedic surgeon. Following the first consultation, additional diagnostic tests are performed (e.g., MRI-scans, x-rays, etc.). Subsequently, another appointment with the neurologist or orthopedic surgeon will follow to discuss the findings. If surgery is indicated, the neurologist can refer patients to the neurosurgeon or orthopedic surgeon. The final decision to perform surgery can be made by the orthopedic surgeon, neurosurgeon or both during a combined consultation. In some hospitals, all patients fill out various patient-reported outcome measures (PROMs) questionnaires prior to this consultation. These PROMs can be used during consultation or for research purposes. The surgeons discuss diagnosis, prognosis, conservative options and surgical options during this consultation. Furthermore, expectations, risks, and outcomes are elaborated upon. If both the surgeon(s) and the patient opt for surgical intervention through lumbar interbody fusion, the patient is

placed on a waiting list. Additional information about hospitalization, surgical technique and the postoperative course can be provided by the healthcare professional. The media through which this information is provided varies per hospital and includes brochures, websites, smartphone applications and consultations with specialized nurses.

2.4.2. Hospitalization and surgery (peri-hospitalization)

The patient is hospitalized one day prior to surgery or on the day of surgery and abstains from food and fluid with a minimum of six hours pre-operatively. The patient is then transferred to the pre-operative holding area for preparations. When the patient enters the operation room, a time-out procedure is carried out by the surgical team, the team consists of an orthopedic surgeon and/or neurosurgeon, an anesthesiologist, a nurse anesthetist, a radiology assistant, surgical nurses and in some cases surgical residents. After the time-out procedure, the patient receives antibiotic prophylaxis, is brought under general anesthesia and positioned in prone position. Surgery is then performed.

2.4.3. Description of surgical technique

A detailed description of the surgical technique is available in Appendix File 4.3. A midline approach is performed, exposing the posterior lumbar elements including the facet joints. Pedicle screws and rods are attached to the back of the vertebra and an interbody fusion spacer (cage) is inserted into the disc space. Autologous bone graft is placed into the interbody space and alongside the back of the vertebra.

2.4.4. Postoperative (peri-hospitalization)

After surgery, the patient is transferred to the recovery room to regain consciousness from anesthesia and receive appropriate postoperative care. A phone call is made by the surgeon to the patients contact person to inform about the procedure. Postoperative pain is managed through pain medication, administered either by patient-controlled analgesia (PCA), or by the nursing staff. The pain medication used, varies per hospital. Once returned to the ward, patients are visited by a doctor or a physician assistant at least once every day. Patients receive deep venous thrombosis prophylaxis according to the local hospital protocol. Furthermore, standardized physical therapy is provided. During postoperative hospitalization, position of the implants will be checked by lumbar spine X-rays. Patients are discharged from the hospital once the pain is acceptable, the wound is dry, safe mobilization is possible and no other complications arise.

2.4.5. Post-hospitalization

During the first six to eight weeks following hospitalization, patients are advised, not to receive extra physical therapy. In these first weeks, functional recovery, reduction of pain, and a reduced need of pain medication is expected. Patients most commonly have consultations with their surgeon at 6 weeks, three months, six months, and twelve months postoperatively, although this is dependent on surgeons' preference. These

consultations are intended to monitor recovery, and if needed, provide additional care (e.g., physical therapy, rehabilitation, medication, etc.). A lumbar spine x-ray can be used to check the position of the implant during one or more of these consultations. If no additional healthcare is needed, patients can be discharged from follow-up.

3. RESULTS

Twenty-seven participants were included: 11 patients (seven males, four females, age ranged from 34-74 years), seven informal caregivers, six surgeons (three orthopaedic surgeons and three neurosurgeons), two specialized nurses, and one nurse consultant.
A total of 2,043 fragments were coded using 34 different codes. To evaluate the process in a comprehensible fashion, results are presented in process' subcategories; "pre-hospitalization", "peri-hospitalization", and "post-hospitalization". Promoting and limiting factors which are discussed during interviews with patients, informal caregivers or healthcare providers are included in Table 4.1 and 4.2.

Table 4.1 - Discussed promoting factors during interviews with patients, ICGs or healthcare providers.

Promoting factor	Patients	Informal caregivers	Healthcare professionals
Information and opportunities to ask question during consultations	X	X	X
Multidisciplinary consultations	X	X	X
Being accompanied by an informal caregiver to consolations	X	X	
Management of expectations	X		X
Good communication and guidance during hospitalization	X	X	X
Mobilization with support of a physical therapist subsequent to surgery	X		X
Post-operative X-ray for later comparison	X		X
Check-up appointments	X	X	X
No unnecessary check-ups after one or two years	X		X
General satisfaction during the process	X	X	X

X = Statement(s) made in compliance with mentioned factor.

Table 4.2 - Discussed limiting factors during interviews with patients, ICGs or healthcare providers.

Limiting factor	Patients	Informal caregivers	Healthcare professionals
Lack of educational material	X	X	X
Long history of complaints and failed conservative treatments	X		X
Long waiting times	X		X
Lack of use of pre-operative PROMs			X
Lack of guidance and communication prior to, during and after hospitalization	X	X	X
Lack of dedicated spine-surgery team on the operation room			X
Lack of standardized pain protocols			X
Limited or delayed involvement of the general practitioner after hospital discharge	X	X	
Lack of information on tapering off opioids	X	X	

X = Statement(s) made in compliance with mentioned factor.

3.1. Pre-hospitalization

All participants reported on the importance of the pre-operative consultation. Patients, informal caregivers and healthcare professionals all stressed the importance of informing the patients about the indication of surgery, alternative surgical and non-surgical treatments, type of surgery, possible complications, and post-operative expectations. Furthermore, the majority of patients reported it was important that the surgeon had sufficient time during consultations, gave clear information and gave opportunities to ask questions.

> *Patient 2, hospital 1; "Eventually, you get so much information, it gets hard to understand everything and keep up. But we got the chance to ask questions."*

Many patients and informal caregivers stated that due to the amount of information, it is beneficial that family or friends can be present during the consultations.

> *Patient 2, hospital 1; "…some things just don't stick, due to the amount of information."*

Additionally, all patients stressed the importance of educational material provided by the caregivers. The media through which additional information is provided varies per hospital: e.g., websites, applications for mobile phones, informational flyers. For patients, the media through which they receive the information did not matter significantly, as long as the amount and quality of the information was adequate.

> *Patient 6, hospital 2; "At some point questions start popping up, and you don't remember what the doctor told you. At these moments, I could just re-read it in the educational material, and I knew what was up."*

In some patients, the lack of information led to patients searching the internet and finding incorrect information or negative patient experiences, causing insecurity about the surgery.

> *Patient 2, hospital 3; "You have got to be careful while searching the internet. If you keep on searching, you only find possible complications, risks… And the stories are all the same; if something goes wrong, your life is virtually over."*

Surgeons and nurses likewise reported that the information provided during consultation should be clear, and additional standardized educational material should be provided in the pre-operative trajectory. The most important aspect of informing the patient pre-operative was to manage and clarify the expectations of the surgery for both patients and informal caregivers and prevent insecurity about the surgery and recovery.

The majority of the interviewed patients had an extensive history of complaints and failed conservative treatments. Many patients stated that not only the physical complaints, but more importantly, the consequences of the complaints on their personal and social life had a significant impact. Restrictions in social life, sometimes even leading to social isolation were frequently mentioned due to progressive pain during walking and mobilization in general. Almost all patients reported that long waiting times were the biggest drawback during the process.

Many patients complained about the long waiting time between consultations, and the months-long waiting lists for surgery.

> *Patient 1, hospital 2; ("What do you think about the waiting time?") "It's horrible. You have to wait two months for a scan, two more months for a consultation with the surgeon, and after that, you still have to wait several months before you finally get the surgery!"*

Several healthcare providers recognized this problem.

> *Healthcare provider 1, hospital 1; "All these patients are in pain, and waiting three or four months is very long when you are experiencing so much pain. At some point they don't know how to deal with it anymore. That's very difficult for me too at times.".*

Numerous patients suggested that it would be favorable to plan multiple consultations or diagnostic procedures on the same day, mainly because driving to and waiting in the hospital can cause more pain. The interviews show that this is a high burden for these patients.

Surgeons reported that it would be advantageous if they had more time for patients during their initial visit. In two hospitals, the neurosurgeon and orthopedic surgeon perform lumbar fusion surgeries in a multidisciplinary team, and likewise have a combined pre-operative consultation for all patients who are potentially indicated for surgical intervention. All these surgeons addressed the added value of this combined consultation in terms of efficiency and expertise. Furthermore, four out of six surgeons advocate multiple consultations or diagnostic procedures on the same day, this would shorten the waiting list and be more efficient for both patients and healthcare providers. The other two surgeons did not make any specific statements on this subject.

> *Surgeon 2, hospital 2; "Ideally, we would work together when doing consultations. So that we can consult the new patients as well as the patients visiting for follow-up, and assess indications for surgery together. Thus, we can maximize our capacity, and prevent multiple, unnecessary visits to the hospital."*

Surgeons stated that the use of pre- and post-operative patient reported questionnaires could be useful to evaluate the quality of provided treatments and for scientific research. There was no consensus whether pre-operative questionnaires could be of added value to the pre-operative consultations. One surgeon stated that looking into the questionnaires

before consultation could aid in getting a general impression of the patients' health, while another surgeon stated that all relevant information is obtained during consultation, suggesting that the clinical relevance of questionnaires is limited.

3.2. Peri-hospitalization

Among patients, there was no evident preference for hospitalization one day prior to surgery, or on the day of surgery. Surgeons preferred hospitalization on the day of surgery. One of the most important factors during hospitalization was communication between patients, informal caregivers, and healthcare providers. According to patients and informal caregivers, information, communication and guidance are especially important in the following situations; initial admission to the ward, preparation for surgery in the holding area, introduction in the operation room, informing patients and their families after surgery.

> *Patient 2, hospital 2; "I would have appreciated some information in the holding and the operation room. Some more guidance in general."*
>
> *Informal caregiver 4, hospital 2; ("Did you receive information about arrangements for informal caregivers during the surgery?") "No, I did not receive any information. ("Did you know where you could wait, eat, drink?") No, we just waited in the public restaurant."*

Furthermore, most patients, informal caregivers and surgeons indicated that it is desirable that the surgeon, who performed the surgery, visits the patient after the procedure.

From the surgeons' perspective, the greatest improvements during surgery would be a dedicated spine team, including scrub nurses, radiology assistants and anesthesiologists. Most delay during surgery is a result of insufficient experience among the team-members. In hospitals where the neurosurgeon and orthopedic surgeon perform lumbar fusion surgeries in a multidisciplinary team, the following possible advantages were cited; shorter surgery time, less door movements, direct quality control, sharing expertise and mutual learning.

Subsequent to surgery, pain medication is given. Although pain management is an essential part of postoperative care, there appears to be a lack of standardization among hospitals. Both patients and healthcare providers emphasized that opioids could be used, although possible side-effects (e.g., constipation, somnolence, nausea), the risk of opioid addiction, and the tapering off should be taken into account.

Most patients are mobilized within the first day after surgery with the help of a physical therapist. Most patients indicated that physical therapists should provide information about mobilization and exercise during hospitalization, preferably both in verbal and in writing. Furthermore, it is important for patients to know which exercises they have to continue after discharge. Besides these exercises, treatment by a physiotherapist is not recommended by healthcare professionals in the first weeks after surgery.

> *Patient 2, hospital 5; "While at the hospital, I was not informed on which type of exercises I should do at home. So, when I was discharged, I tried some exercises with my own*

> *physiotherapist. Unfortunately, that made matters worse. I did not receive educational material on the subject either, so I searched the internet and found spine-surgery specific exercises from other hospitals."*
>
> *Surgeon 1, hospital 4; "I would like to guide the patients during the whole process. Right now, it seems rather black and white. If you advise physical therapy, the therapists tend to give back-specific exercises, which is undesirable in the first weeks after surgery. But it would be beneficial if the patients received some additional help with mobilization and general physical exercise in these weeks."*

All patients received an x-ray of the lumbar spine post-operatively. Surgeons used them mainly as a baseline image for comparison, if future imaging is needed.

Patients and informal caregivers indicated that it was preferable to know what kind of difficulties they could expect in daily life when the patient was discharged. Furthermore, all patients emphasized the value of knowing who to turn to with questions. They stated that it could be beneficial if there is a dedicated contact person in the hospital for questions about the surgery and recovery.

> *Informal caregiver 5, hospital 2; ("If something would have gone wrong, did you know who the contact person was?") "No, I did not know who the contact person was."*
>
> *Patient 2, hospital 2; ("Do you mean that some more guidance would be better? Having a dedicated contact person to turn to with questions?") "Yes, that sums it up, more guidance throughout the whole process."*

Additionally, the transfer of medical information to the patients' general practitioner should ideally take place within the first days after discharge so that he/she is fully aware of the physical condition of the patient in case any support is necessary.

3.3. Post-hospitalization

Patients and informal caregivers reported that the first days at home were the toughest; the wound could be painful, mobilization was challenging and most patients needed assistance with housekeeping and self-care activities involving bending, leaning, or lifting heavy objects. Though informal caregivers acknowledged that they had a large share in patient-related care and additional household tasks, most did not experience the first week at home as troublesome. Many patients cited that finding the right balance between activity and rest was challenging.

Comparable to the peri-hospitalization period, patients are in need of information, communication and guidance. Recurring topics of insecurity were pain medication, tapering off opioids, wound healing, sutures, exercise, expectation management and hospital appointments. Once again, patients preferred adequate information in verbal and in writing about these topics. A direct contact person was stated as helpful and pleasant if patients had any unanswered questions. Furthermore, it was advantageous if the general practitioner is actively involved in the post-operative care, especially for tapering off opioids.

> *Patient 2, hospital 1; "It is startling how fast you can get addicted to those pills, even if you are familiar with the problem."*

Several patients, surgeons and nurses pointed out that healthcare-initiated contacts by phone, to obtain information about the patient and to answer questions, could be helpful in the first few weeks after surgery. In hospitals in which patients were actively contacted by a dedicated contact person during the first weeks after surgery, most patients made positive statements about this extra care. In hospitals in which no dedicated contact person was present, patients were more uncertain about who to turn to with questions, and their recovery in general.

From the surgeons' perspective, the follow-up appointments six weeks and three months after surgery are the most significant. If the recovery is progressing as expected, further follow-up is only needed on indication. From the patient's perspective, reassurance and final closure of the healthcare process are the most frequently mentioned factors determining satisfactory ending of the follow-up. Some patients mentioned that radiography could be helpful to assure that the implants were still in place, and the recovery was advancing as to be expected. Most patients agree to not having one- and 2-year follow-up after surgery, as long as they are assured that their recovery is acceptable, and as long as they know who to contact to when problems arise.

Aside from the negative experiences and suggestions for improvement, patients were in general satisfied about the process of the lumbar fusion surgeries, including the pre-hospitalization, peri-hospitalization and post-hospitalization phase. Most stated that the pre-operative pain was significantly reduced, and the surgery had a positive impact on their life.

> *Patient 2, hospital 1; "When I returned to the hospital after the surgery, I told the surgeon he performed a miracle. Nothing more, nothing less. They make the difference between living your life and sitting on the side-line."*

4. DISCUSSION

This study is one of the first qualitative studies about the process surrounding lumbar fusion surgery, incorporating input from patients, informal caregivers and healthcare professionals from multiple hospitals. Results of our study described several promoting and limiting factors of the lumbar fusion surgery process. The most frequently mentioned promoting factors were; information and opportunities to ask questions during consultations, multidisciplinary consultations, good communication and guidance during hospitalization, and the use of several follow-up appointments. The most frequently mentioned limiting factors were; lack of educational material, lack of guidance and communication prior to, during, and after hospitalization.

Previous qualitative studies on lumbar fusion processes are limited. However, studies concerning some of the abovementioned promoting and limiting factors for different disciplines are available. The study of Murtagh et al., a qualitative study focused on improving the consultation process, for instance, found that patients were more likely to ask questions if doctors actively involve patients. For example, showing and discussing

scans or x-ray results during consultation[11]. Furthermore, two studies showed that cohesive teamwork resulted in improved communication between healthcare workers, decreased the number of adverse events, improved patient related outcomes and increased work-satisfaction among the medical staff[12,13].

Although patients, informal caregivers and healthcare providers all endorse the importance of follow-up appointments after discharge, there is a lack of evidence for the need of a post-operative follow-up after spine surgery[14]. Hospital follow-up appointments do not appear to improve readmission rates or survival in general medicine patients[15]. At last, a recent review on perioperative patient satisfaction concluded that, in order to enhance patient satisfaction, healthcare providers should focus on communication and providing information[16], which is in accordance with the results of our study.

The outcomes of our study are in line with the results of a previously published study by Damsgaard et al.[6]. They focused on how patients experience their situation from the point of making the decision to undergo spinal fusion surgery, to living everyday life after spinal fusion surgery. They concluded that spinal fusion surgery initiates hope for less pain, but also creates a feeling of insecurity for life after surgery, as patients were accustomed to a life with complaints. In our study, patients likewise addressed that insecurity about the surgery and the recovery played a significant role in their experiences. In concordance with our results, Damsgaard et al. found that providing information and clear communication between patient and healthcare provider were key-factors in the process from indication for surgery to recovery.

Two other qualitative studies pointed out that the long pre-operative illness process, the tumultuous recovery and unfulfilled or unrealistic expectations about the surgery were frequently reported by patients undergoing spinal fusion surgery[7,8]. Our present study underlines comparable problems; insecurity about complaints, surgery, and recovery. Additionally, our study provides possible solutions or suggestions for improvement based on input from patients, informal caregivers and healthcare providers; clear preoperative information about the surgery, expectations and postoperative period, both verbally and in writing (paper, websites, mobile phone applications) could be helpful. Furthermore, a dedicated healthcare professional, for example, a nurse practitioner trained in fusion surgeries, could be beneficial in the guidance of these patients. Judging the results of this study, these solutions might increase patient-satisfaction.

One suggestion for pre-operative improvements of patients and informal caregivers was planning several appointments on one day. Practically, this could be attained in the form of a "one stop shop solution", in which several medical specialists (e.g., neurologist, neurosurgeon, orthopedic surgeon) are consulted in succession. Another practical solution could be using dedicated diagnostic slots (e.g., MRI, CT, x-ray) on days that carrousel consultations are planned. It should be noted that in some cases, spreading different appointment over several weeks or months is unavoidable or even necessary from a healthcare perspective.

The greatest area for improvement during surgery from the surgeons' point of view would be a dedicated spine-surgery team. In practice, this would mean that a pool of dedicated surgical nurses, radiology assistants, anesthesiologists and nurse anesthetists is formed. Having a dedicated spine-surgery team could lead to standardization of the surgical process, shorter surgery time, and possibly lower complication rates[17]. Furthermore, having a protocolized pain treatment during and after surgery, could lead to improved pain-management. Moreover, having a standardized pain treatment protocol could result in informing and educating patients more clearly on the risks and side-effects of pain medication, and how to taper off these medications after surgery.

Although this study focusses on lumbar fusion surgery, results can be translated to other fields of spine surgery and surgery in general. Themes like providing information and guidance, communication and expectation management are topics known to be important in most fields of surgery. We hypothesize that the importance of the promoting and limiting factors found in this study are of greater importance as the complexity of surgical interventions increase. Furthermore, multidisciplinary consultations, specialized operation room staff and a dedicated contact person (e.g., a specialized nurse) might only be feasible in highly complex care.

Part of our study was carried out during the COVID-19 pandemic. This led to some patients having follow-up appointments through either telephone or video-conference (telehealth). Surprisingly, these patients made positive comments about the use of telehealth. Some patients who were interviewed prior to the COVID-19 pandemic likewise stated that, in specific situations, telehealth is preferred. It was pointed out that it could be beneficial to talk to the doctor, without the need to physically go to the hospital. This was especially the case for patients with a quick recovery. Surgeons were equally enthusiastic about the use of telehealth. Technical difficulties with the communication system did not pose a significant problem. These results were similar to the results of a large study of Isautier et al. about patient satisfaction with telehealth during the COVID pandemic[18].

A possible limitation of this study is that qualitative research incorporating interviews is always susceptible to interpretation by the researchers. To limit personal interpretation and to increase reflexivity, we; 1) included participants from different perspectives and different hospitals; 2) used open-ended questions and asked for additional information; 3) anonymized and transcribed all interviews; 4) coded and analyzed text files using computer software; 5) periodically reflected on the data, used codes and categories. To limit inter-observer variability, transcribing, coding and analyzing were carried out by two researchers (RD and IC)[19].

Another limitation of this study is the fact that this qualitative research is carried out as a part of a randomized controlled trial conducted in multiple hospitals in The Netherlands. This led to two study-specific questions and topics being discussed in the interviews with surgeons. These fragments are not relevant nor useful for the process evaluation of lumbar interbody fusion surgery, and were therefor not included in this study. Additionally, the evaluation of this healthcare process in the Netherlands might have

impact in the possibility to generalize some findings of our study, as various strengths and limitations in the process could be specific for the Dutch healthcare system. Vice versa, some relevant strengths and limitations which are present in healthcare systems outside of The Netherlands cannot be identified by our study due to the study-design.
Furthermore, the questions used in the interviews are not validated. It is possible that the open-ended questions biased the responses of the participants in some way. However, these open-ended questions were formed based on participant observations by researchers attending and observing the process during outpatients' clinics and hospital admission.
Strengths of this process evaluation are the relatively large number of interviews with patients, informal caregivers and healthcare providers from five hospitals[6-8]. By obtaining valuable insights in the perceived health, impact of illness and treatment, and the experiences of patients, informal caregivers and professional healthcare providers, this study culminates in a more complete and in-depth understanding of the total process.

5. CONCLUSION

This study is one of the first qualitative studies about the process surrounding lumbar fusion surgery, incorporating input from patients, informal caregivers and healthcare professionals. Overall, all participants were satisfied with the current healthcare process in lumbar fusion surgery. However, we found that lack of educational material and guidance during the process led to insecurity about complaints, surgery, and recovery. To improve the process of lumbar interbody fusion and to increase patient satisfaction, healthcare providers should focus on guiding and educating patients and informal caregivers about the pre-operative trajectory, the surgery, and the recovery. This can be accomplished by informing patients and informal caregivers both verbally, and in writing (paper, websites, mobile phone applications) or by a dedicated contact person (e.g., nurse practitioner). From the healthcare providers perspective, the process could be improved by multidisciplinary consultations and a dedicated spine team on the operation room.

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APPENDIX FILE 4.1 - INTERVIEW GUIDES

Checklist Physician Assistant/Specialized Nurse:

- **Preoperative:**
  - Which type of patients are seen in the outpatient clinic?
    - Spondylodesis?
    - How many visits to outpatient clinic?
  - Who refers the patients to you?
  - How do you evaluate the transfer of medical information?
  - What information do you provide the patients?
    - Preoperative
    - What is the added value in comparison with consultations by a surgeon?
    - Process of hospitalization
    - Postoperative
  - Are informal caregivers and/or family involved?
  - Use of patient reported questionnaires in outpatient clinic?
  - Use of educational material?
    - Flyers
    - Websites
  - Do you see all patients who receive spodylodesis?
  - Do you get feedback form patients on this consultation?
  - What are common preoperative problems for patients?
    - How are these problems solved?
  - Do you also provide this extra care for other types of surgery?
  - Are there other things you arrange for?
    - Logistic problem solving?
  - Do you have any suggestion for improvement in the preoperative trajectory?
- **Surgery:**
  - Are patients hospitalized one day prior to surgery?
    - Patients' experiences?
    - Do you have any specific tasks during surgery?
  - Tasks on day of surgery?
  - Do you speak with informal caregivers during first hospitalization and surgery?
- **Hospitalization:**
  - What are common peri-hospitalization problems for patients?
    - Are there ways to solve these problems?
  - Tasks during hospitalization?
    - Do you assist/function as the ward physician?
    - Arrangements of post-hospitalization care?

    - Do you visit hospitalized patients after surgery?
    - Do you arrange homecare if necessary?
  - Do you have any suggestion for improvement in the peri-hospitalization trajectory?
- **Post-hospitalization:**
  - Do you see patients in the outpatient clinic after surgery?
    - Wound assessment?
    - Other assessments?
    - How many times do you see patients in the outpatient clinic after surgery?
    - In which cases do you consult the surgeon or supervisor?
    - Is patients have question in between visits, who can they contact?
  - Frequently asked questions by patients?
    - How can we overcome/answer these questions?
  - What information do you provide the patients post-hospitalization?
    - Fragmin
    - Physical therapy
    - Exercise
    - Sutures
    - Pain medication
    - Homecare
  - Use of patient reported questionnaires in outpatient clinic?
  - Do you have any suggestion for improvement in the post-hospitalization trajectory?
  - Do informal caregivers play a significant role in the postoperative care? Do we underestimate the amount of help informal caregivers provide?
  - Do patients report on common problems?
    - Subsequent to surgery
    - Long term
    - Possible solutions?
  - Do you have any suggestion for improvement in the post-hospitalization trajectory?

Checklist patients

- **Preoperative:**
- Visits to outpatient clinic before surgery:
  - How many visits?
    - Transfer of medical information
    - Waiting time
  - What information did you receive?

    - Different treatment options
    - Complications
    - Expected period of recovery
    - Expectations regarding treatment (leg pain vs. backpain)
    - Was the surgical intervention clearly explained?
    - What will be done?
    - How long will the surgery take?
    - General anesthesia
    - Pain medication with morphine pump or oral medication
  - Use of educational material
    - Flyer
    - Websites
  - Were all consultations useful?
  - Did you remember the important information?
    - Were difficult terms used, was everything explained in an understandable fashion?
  - Were there enough opportunities to ask questions?
  - Do you have any suggestion for improvement in the pre-hospitalization trajectory?
- **Surgery**:
  - General remarks about day of surgery?
    - How did you experience the admission to the ward?
    - How were you prepared for surgery?
    - How did you experience the transfer to the holding?
    - How did you experience the preparations for anesthesia?
    - How did you experience the interaction in the operating room prior to surgery?
    - Accompaniment
    - Medical information transfer
    - Identification of patient
    - Was it clear why everyone was there and what everyone's role was during surgery?
  - Positive/negative experiences?
  - Do you have any suggestion for improvement?
- **Hospitalization:**
  - How long did you have to stay hospitalized?
  - Experiences?
    - Which doctors did you see during hospitalization?
    - Ward doctor, surgeon?
    - Responsible surgeon(s)?

    - Experience with different doctors
    - Was it clear to you what role each healthcare professional had?
  - Go through protocol:
    - Wound examination
    - Physical therapy (Day after surgery, climbing stairs, educational material about physical therapy)
    - Pain medication (pump, sufficient, pain management, tapering off medication)
    - Fragmin (6 weeks?)
    - X-ray of the lumbar spine during hospitalization?
    - Corset?
  - Information about post-hospitalization trajectory and homecare arranged if necessary?
    - Fragmin
    - Physical therapy
    - Exercise
    - Sutures
    - Pain medication
    - Homecare
    - Medical rehabilitation
  - Did you remember the important information?
    - Were difficult terms used, was everything explained in an understandable fashion?
  - Were there enough opportunities to ask questions?
  - Do you have any suggestion for improvement during hospitalization?
- **Post-hospitalization:**
  - What were the first days at home?
  - Did you need any help?
    - Medication (Pain medication, fragmin).
    - Physical therapy
    - Homecare
    - Medical rehabilitation
    - Sufficient care?
  - Setting goals and achieving them (what were the biggest obstacles or barriers)
    - Did you recover as you expected?
  - How many times do you visit the outpatient clinic after surgery?
    - Wound examinations?
    - Visits with the responsible surgeon
    - Recovery
    - Goals and difficulties

    - X-ray
    - Follow-up appointments
  - Useful?
  - Did you remember the important information?
    - Were difficult terms used, was everything explained in an understandable fashion?
  - Do you have any suggestion for improvement during hospitalization?
  - Do you think outpatient visits 6 and 12 months after surgery are useful?

Checklist informal caregivers

- **Preoperative:**
  - Visits to outpatient clinic before surgery
  - Were you present at all appointments?
  - What are your experiences?
  - What information did you receive?
    - Were difficult terms used, was everything explained in an understandable fashion?
    - Complications
    - Expected period of recovery
    - Expectations regarding treatment (leg pain vs. backpain)
    - Was the surgical intervention clearly explained?
    - What will be done?
    - How long will the surgery take?
    - General anesthesia
    - Pain medication with morphine pump or oral medication
  - Were all consultations useful?
  - Did you remember the important information?
    - Were difficult terms used, was everything explained in an understandable fashion?
  - Were there enough opportunities to ask questions?
  - Do you have any suggestion for improvement in the pre-hospitalization trajectory?
- **Surgery:**
  - Were you informed about the surgery?
    - Communication
  - How did you experience the day of surgery?
    - Which services were provided?
    - Were you informed about services you could use?
  - Do you have any suggestion for improvement?
- **Hospitalization:**
  - Experiences?
    - Which doctor did you see during hospitalization?

    - Experience with different doctors
    - Was it clear to you what role each healthcare professional had?
  - Did you receive information about the post-operative care?
    - Were you involved in the postoperative care?
  - Useful services for informal caregivers?
    - Were you informed about services you could use?
    - What went well?
    - What would have been usefull?
  - Do you have any suggestion for improvement?
- **Post- hospitalization:**
  - Did you have a significant role during recovery?
  - Did you receive enough support/help with providing care (e.g. fragmin)?
  - Do we underestimate the amount of help informal caregivers provide?
  - Were you present at postoperative outpatient clinic visits?
  - Experiences?
  - Useful?
  - Did you remember the important information?
    - Were difficult terms used, was everything explained in an understandable fashion?
  - Were there enough opportunities to ask questions?
  - Do you have any suggestion for improvement in the post-hospitalization trajectory?
  - Do you think outpatient visits 6 and 12 months after surgery are useful?

Checklist surgeons

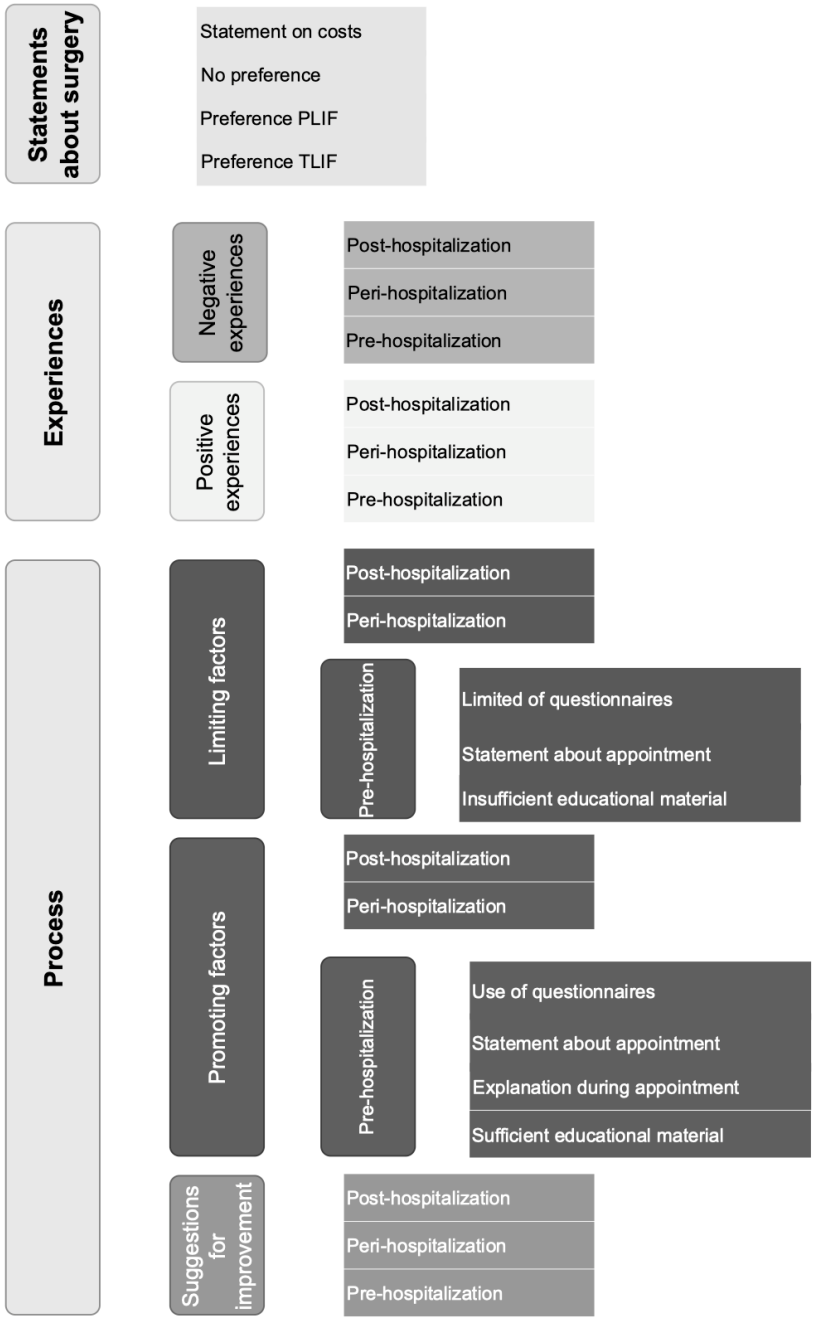
- **Preoperative:**
  - How many times do you see a patient before surgery?
  - How much time do you have every visit?
  - What information did you give the patients?
    - Different treatment options
    - Complications
    - Expected period of recovery
    - Expectations regarding treatment (leg pain vs. backpain)
  - Patient reported questionnaires in outpatient clinic?
    - Do you use them?
    - Are they useful?
    - Do you have questionnaires on the pain experience?
  - Use of educational material?
    - Flyers
    - Websites
  - Are all visits useful?

  - Do you have any suggestion for improvement in the pre-hospitalization trajectory?
- **Surgery:**
  - Preference for TLIF or PLIF?*
    - Why?
  - Would you consider choosing the most cost-effective alternative?*
    - Why?
  - How do you plan surgeries? How do you optimize the process and use time effectively?
    - Do you perform the surgery alone or with two surgeons? (Neurosurgeons/orthopedic surgeon)
    - Room for improvement?
    - Time schedule of surgery
    - How long does the surgery take?
    - How do you manage these types of surgery?
    - Room for improvement?
  - Radiology
    - Which system is used?
    - When is radiology performed? How long does it take?
    - How do you manage the imaging?
    - Room for improvement?
  - Door movement
    - Strict policy
    - Room for improvement?
- **(Post) Hospitalization:**
  - How many times and at what interval do you want patients to visit the outpatient clinic after surgery?
    - Wound examinations?
    - How is this interval chosen?
    - Is this recorded in protocols?
    - Do you use (radiographic) imaging? When and why?
  - Visits 1- and 2-year post-operative?
    - Why or why not??
    - Useful?
  - Questionnaires
    - Useful?
    - How do you use the outcomes?
  - How is the post-hospitalization care arranged?
    - Do you visit the hospitalized patient after surgery?

    - Which types of additional care are needed (e.g., physical therapy)?
  - Do you have any suggestion for improvement in the (post)hospitalization trajectory?

* Study-specific questions. Fragments regarding these questions are not relevant nor useful for the process evaluation of lumbar interbody fusion surgery, and were therefor not included in this study.

APPENDIX FILE 4.2 - LIST OF CODES FOR DATA-ANALYSIS



APPENDIX FILE 4.3 - DETAILED DESCRIPTION OF SURGICAL TECHNIQUE

Description of surgery

A midline approach is performed, exposing the posterior lumbar elements including the facet joints. Pedicle screws are placed bilaterally, using fluoroscopic guidance or navigation, depending on preference of the surgeon.
TLIF: Unilateral exposure to the intervertebral disc is assured by unilateral facetectomy, decompressing the descending and leaving roots. In case of bilateral symptomatic leg pain, the side of the unilateral approach is free of choice for the surgeon. Unilateral facetectomy is performed to gain access to the intervertebral disc. After removal of the intervertebral disc, endplate cartilage is prepared to provide a host bed of bleeding subchondral bone for placement of the intercorporal cage. The TLIF cage size is determined by a trial cage and checked by fluoroscopy. The definitive cage is filled with autologous bone or allograft and is tamped into place. Its final position is checked radiological. After placement of the TLIF cage, the remainder of the disc space is filled with autologous bone, obtained from the decompression. A titanium rod interconnects the screws on each side. In several hospitals, epidural analgesia is administered. The spreader is removed and the wound is thoroughly irrigated and closed in several layers without suction drainage.
PLIF: Bilateral access to the intervertebral disc assured by medial facetectomy. The intervertebral disc will be removed bilaterally. Subsequently, endplate cartilage is prepared to provide a host bed of bleeding subchondral bone for placement of the cages. Before placement of the definitive cages, the disc space is partially filled with autologous bone, obtained from decompression. Cages will be placed bilateral after determination of cage size by trail cages and fluoroscopy. These are also filled with autologous bone or allograft and are tamped into place with fluoroscopic guidance. Their position is checked radiological. A titanium rod interconnects the screws on each side. In several hospitals, epidural analgesia is administered. The spreader is removed and the wound is thoroughly irrigated and closed in several layers without suction drainage.

CHAPTER 5

COST-EFFECTIVENESS OF OPEN TRANSFORAMINAL LUMBAR INTERBODY FUSION (OTLIF) VERSUS MINIMALLY INVASIVE TRANSFORAMINAL LUMBAR INTERBODY FUSION (MITLIF): A SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT

Background context
The number of performed instrumented lumbar spine surgeries and associated healthcare-related costs have increased over the last decades, and will increase further in the future. With the consistent growth of healthcare-related costs, cost-effectiveness of surgical techniques is of major relevance. Common indications for instrumented lumbar spine surgery are spondylolisthesis and degenerative disease. A commonly used technique is the open transforaminal lumbar interbody fusion (OTLIF). Nowadays, there is an increasing interest in the minimally invasive variation of this technique (MITLIF). Currently available literature describes that MITLIF has comparable or even better clinical results compared to OTLIF. Cost-effectiveness of MITLIF and OTLIF is important considering the growing health-care related costs, although no consensus has been reached regarding the most cost-effective technique. In this systematic review, previous literature concerning costs and cost-effectiveness of OTLIF was compared with MITLIF in patients with lumbar spondylolisthesis or degenerative disease. Furthermore, methodological quality of included studies was assessed.

Purpose
This study aims to evaluate the current literature on cost-effectiveness of open transforaminal lumbar interbody fusion (OTLIF) compared to minimally invasive transforaminal lumbar interbody fusion (MITLIF) in patients with lumbar spondylolisthesis or degenerative disease.

Study design
This study is a systematic literature review and meta-analysis.

Study sample
Clinical studies reporting costs or cost effectiveness for either OTLIF or MITLIF in patients with spondylolisthesis, lumbar instability, or degenerative disease were included.

Outcome measures
The following data items were evaluated: study design, study population, utility measurement tool, gained Quality Adjusted Life Years (QALYs), cost sources, health care and societal perspective costs, total costs, costs per QALY (cost-effectiveness) and incremental cost-effectiveness ratio (ICER).

Methods
A systematic search was conducted using databases PubMed, CINAHL, EMBASE, Cochrane, Clinical Trials, Current Controlled Trials, NHS Centre for Review and Dissemination, Econlit and Web of Science on studies reporting OTLIF or MITLIF,

spondylolisthesis or lumbar instability or degenerative disease, and costs. Relevant studies were selected and reviewed independently by two authors. For comparison, all costs were converted to American Dollars with the reference year 2018.

Results

After duplicate removal, a total of 892 studies were identified. Eventually, 32 studies were included. Nine studies compared OTLIF and MITLIF directly. All studies mentioned healthcare perspective costs. Seven studies mentioned societal perspective costs. Cost-effectiveness of OTLIF was mentioned in five studies, ranging from $47,303/QALY to $218,766/QALY. Cost-effectiveness of MITLIF was mentioned in one study, $121,105/QALY. Meta-analysis of hospital perspective costs showed a significant overall effect in favor of MITLIF, with a mean difference of $2,650. There was great heterogeneity in health care and societal perspective costs due to different in-, and exclusion factors, baseline characteristics, and calculation methods. Overall quality of studies was low.

Conclusions

OTLIF and MITLIF appear to be expensive interventions when using a threshold of $50,000/QALY. Results of this study and previous literature suggest that MITLIF is more cost-effective compared to OTLIF. Considering the increase in healthcare costs of instrumented spine surgery, cost-effectiveness could be one of the factors in surgical decision-making. Prospective randomized studies directly comparing cost-effectiveness of OTLIF and MITLIF from both hospital and societal perspectives are needed to obtain higher level of evidence.

1. INTRODUCTION

Since 1980, the global population of people older than 60 years has doubled. This number is expected to double again by 2050[1]. The ageing population is one of the most prominent factors by which the number of instrumented spine surgeries has increased and will even increase further in the future[2,3]. This results in higher healthcare-related costs. Previous studies, concerning the national US bill for instrumented spine surgery, have shown a 7.9 fold increase between 1998 and 2008 and a 2.8 fold increase between 2004 and 2015[4,5]. To limit the increase of healthcare-related costs concerning instrumented spine surgery in an ageing population, medical practitioners should consider the most cost-effective surgical technique[6,7]. Notwithstanding that surgical experience, availability of the surgical technique and surgical indication are prioritized factors in surgical decision making.

Common indications for instrumented lumbar spine surgery are lumbar spondylolisthesis and degenerative disease. Spondylolisthesis is an instability as a result of facet joint degeneration or lysis in the pars articularis, resulting in slippage of the upper vertebra over the underlying vertebra [8]. Lumbar degenerative disease is caused by disc degeneration and is a major cause of back pain and associated disability, especially in aged individuals[9,10]. Lumbar spondylolisthesis and degenerative disease can cause back pain, neurogenic claudication and lumbar radiculopathy. Instrumented spine surgery can be performed to relieve complaints and restore spinal stability. A widely used surgical technique is the open transforaminal lumbar interbody fusion (OTLIF). In OTLIF, a unilateral transforaminal approach with unilateral facetectomy is used to insert a single cage. Although, several surgeons might prefer bilateral decompression. Additionally, posterior pedicle-screw fixation is performed[11]. A newer, minimally invasive variation to this technique (MITLIF) is gaining popularity. In MITLIF, decompression and cage insertion are performed through tubular retractors, followed by percutaneous posterior pedicle-screw fixation. Previous literature generally describes comparable or improved clinical effectiveness for MITLIF compared to OTLIF. Furthermore, studies reported significantly less blood loss, less complications and shorter duration of hospitalization associated with MITLIF compared to OTLIF. The difference in operating room time remains unclear[12-16].

Comparable clinical outcome, but lower blood loss, shorter duration of hospitalization, lower pharmacy and laboratory costs, lower implant costs and lower physical therapy costs could result in MITLIF being more cost-effective compared to OTLIF. Hitherto, no insight has been attained regarding the cost-effectiveness, although this is of importance regarding rising healthcare-related costs. This systematic review aimed to evaluate the current literature on cost-effectiveness of MITLIF compared to OTLIF in patients with lumbar spondylolisthesis or degenerative disease. Furthermore, methodological quality of the included studies was assessed and taken into account.

2. MATERIALS AND METHODS

2.1. Review protocol

This systematic review was executed in accordance with the PRISMA statement and the five-step approach on preparing a systematic review of economic evaluations by Van Mastrigt et al.[17-21].

The review protocol consisted of a research question, search strategy and eligibility criteria for assessing full-text studies. The research questions were formulated as follows:

1. Is minimally invasive transforaminal lumbar interbody fusion (MITLIF) in adults with lumbar spondylolisthesis or degenerative disease more cost-effective than open transforaminal lumbar interbody fusion (OTLIF)?
2. What is the methodological quality of the included studies?

2.2. Search strategy and eligibility criteria

A systematic search of databases PubMed, CINAHL, EMBASE, Cochrane, Clinical Trials, Current Controlled Trials, ClinicalTrials.gov, NHS Centre for Review and Dissemination, Econlit, and Web of Science was conducted without using filters. Furthermore, reference lists of cost-effectiveness studies for either OTLIF or MITLIF were manually searched for additional studies. Detailed search strategies for each database are available in Additional File 5.1, included in the appendix. Our last search was conducted on April 3rd, 2020. Studies were included if they met all of the following eligibility criteria: (i) OTLIF (open transforaminal lumbar interbody fusion) and/or MITLIF (minimally invasive transforaminal lumbar interbody fusion), (ii) lumbar spondylolisthesis and/or lumbar instability and/or degenerative disease, (iii) cost.

2.3. Study selection and data collection process

Selection of studies was performed by two authors (RD and SH). Duplicates were removed, potentially eligible studies were screened on title and abstract, and full texts were assessed using abovementioned eligibility criteria. Data were collected using a prospectively designed data collection sheet. Data were independently extracted by two authors (RD and SH). The following data items were considered: study design, study population, utility measurement tool, gained Quality Adjusted Life Years (QALYs), cost sources, health care and societal perspective costs, total costs, costs per QALY (cost-effectiveness) and incremental cost-effectiveness ratio (ICER). If necessary, consensus was reached between both authors through discussion or with assistance of a third reviewer (IC). The complete data collection sheet can be found in Additional File 5.2 in the appendix.

To determine cost-effectiveness, difference in total costs have to be divided by difference in QALY-gain. Total costs can be determined using both health care perspective costs (costs for health care resources that an intervention requires, like operating room time)

and societal perspective costs (all resource costs associated with an intervention, including costs for caregiver time or absenteeism)[22].
All costs were converted to American Dollars with the reference year 2018 with the use of a web-based tool developed by the Campbell and Cochrane Economics Methods Group (CCEMG) and the Evidence for Policy and Practice Information and Coordinating Centre (EPPI-Centre) (v.1.6)[23]. If the index year was not mentioned in the study, the last year of patient inclusion was used for this calculation. Subsequently, if the last year of patient inclusion was not described, the year of publication was used as index year.

2.4. Quality assessment

Two authors (RD and SH) performed quality assessments on the included studies. Risk of bias was assessed with the bias assessment tool of Cochrane Handbook for Systematic Reviews of Interventions[24]. Risk of bias was based on different domains; confounding, selecting patients, classification of interventions, deviation from intended intervention, missing data, measure outcome, selection of the reported results and other types of bias. Criteria were scored with "low", "high" or "unclear" risk of bias for randomized studies, and "low", "moderate", "serious" or "unclear" risk of bias for non-randomized studies. Levels of evidence were determined with guidelines of Oxford Centre for Evidence-based Medicine (2011)[25] and are summarized in Additional File 5.3 in the appendix. Methodological quality of economic evaluations was analyzed using The Consensus Health Economic Criteria (CHEC) list[26]. Full risk of bias assessment sheets and CHEC list scores can be found in Additional File 5.4 and Additional File 5.5 in the appendix. Consensus was reached between both authors through discussion.

2.5. Meta-analysis

A meta-analysis of the study data was performed using the Cochrane Collaborations Review Manager version 5.3[27]. A meta-analysis was conducted for outcomes of which data were sufficiently reported.
Calculations were performed using Random Effects, Fixed Effects, Mean Difference and a 95% Confidence Interval (CI). P values ≤ 0.05 were regarded as statistically significant. We quantified heterogeneity between studies using the I^2test. Heterogeneity was regarded as low with an $I^2 \leq 50\%$, moderate with a $50\% < I^2 < 75\%$, and high with an $I^2 \geq 75\%$.
An incremental cost-effectiveness ratio (ICER) was estimated for studies providing sufficient data. Necessary data for an ICER estimation are differences in costs and differences in clinical effectiveness, usually expressed in QALY gain. ICER = (C1 – C0) / (E1- E0). C1 and E1 indicate costs and effectiveness of the intervention group, whereas C0 and E0 indicate costs and effectiveness of the control group.

2.6. Protocol registration

This review protocol has been registered in the PROSPERO Database[28].

3. RESULTS

3.1. Study selection

The systematic database search resulted in 1405 studies. Three additional studies were identified through manual searches of relevant reference lists. After removing duplicates, 892 studies were screened on title and abstract. Sixty-six studies were eligible for full-text analysis, resulting in exclusion of 34 studies; 17 studies did not describe one of the interventions of interest, 11 studies did not report the outcome of interest, three studies used similar patient cohorts, two studies did not include patients with lumbar spondylolisthesis or degenerative disease and for one study full text was unavailable. Results of the study selection process are summarized in Figure 5.1.

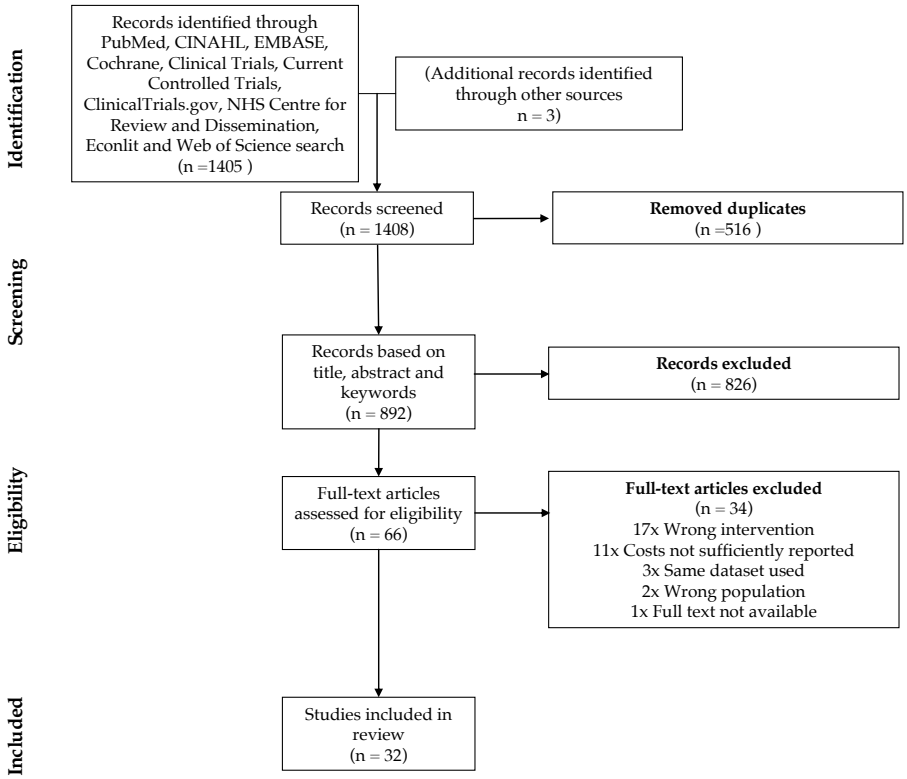

Figure 5.1 - PRISMA Flowchart.

3.1. Study characteristics

Study characteristics of the 32 included studies are summarized in Additional File 5.3 in the appendix.

Thirteen studies were cost-effectiveness studies[29-41] and 19 were financial studies [42-60]. Reported costs varied from implant costs only, to all resource costs associated with an intervention, including costs for caregiver time or absenteeism. Publication years ranged from 2001 to 2020. Follow-up time ranged from time of hospitalization to four years postoperative. Twenty-two studies were performed in the United States of America[29,30,32-39,41,43,45-47,50,51,53,54,56-58], five in China[42,44,55,59,60], two in Europe (Denmark and Turkey)[31,48], one in Canada[40], and one in Iran[49].

Nine studies compared OTLIF and MITLIF directly[32,37,38,40,51,53,54,56,58]. Thirteen studies compared OTLIF with other instrumented spine surgery techniques[31,33,35,36,41,42,46,48-50,57,59,60], two studies described costs of OTLIF without comparative cohort[29,39]. Seven studies compared MITLIF with other instrumented spine surgery techniques[30,34,43-45,52,55], and one study described costs of MITLIF without comparative cohort[47].

All studies reported healthcare perspective costs. The cost-sources included hospital databases, Medicare (official site of the U.S. Government), Current Procedural Terminology Codes (CPT Codes), Diagnosis-Related Group Codes (DRG Codes), Redbook (drug pricing resource) and National health insurance registers. Healthcare perspective costs were mostly determined by using actual hospital costs. However, in seven studies (one OTLIF-, versus MITLIF-study, and six OTLIF-studies), healthcare perspective costs were determined using charges (amount paid by patient or insurance)[33,50,57] or a combination of costs and charges[36,41,46,53].

Societal perspective costs were described in two studies comparing OTLIF and MITLIF directly[37,38], and five studies comparing OTLIF with other surgical techniques[29,31,33,36,39]. To determine societal perspective costs, one Danish study used the DREAM database to determine societal perspective costs based on productivity losses[31]. The DREAM Group is a governmental institution that conducts statistical and descriptive analyses of the Danish economy[61]. The other six studies included missed working days to estimate productivity losses[29,33,36-39]. Additionally, two of these studies included unpaid caregiver opportunity costs[29,36], one study included missed homemaking days in patients with housekeeping as primary activity[37] and two studies included both[38,39]. In all six studies, costs for missed days of unpaid caregivers were estimated based on average gross wages plus non-health benefits. The hours of missed work were patient-reported through either a questionnaire or an interview. Using the standard human capital approach, costs were estimated by multiplying the change in hours worked by the gross-of-tax wage rate based on self-reported wages at study entry.

Eleven studies used SF-6D, EQ-5D, or the Oswestry Disability Index (ODI) to determine mean or cumulative QALY gain, whereof four studies comparing OTLIF and MITLIF directly[32,37,38,40] and seven OTLIF-studies[29,31,33,35,36,39,41]. Cost-effectiveness was calculated in five studies, one study comparing OTLIF and MITLIF[40] and four OTLIF-studies[29,33,36,39].

3.2. Quality of identified studies

Methodological quality assessment can be found in Additional Files 5.4 and 5.5 in the appendix. Based on the criteria for randomized studies, all three randomized studies had a high risk of bias, mainly due to lack of blinding[31,55,60]. Based on the criteria for nonrandomized studies, three nonrandomized studies had a serious risk of bias[29,50,57] and the remaining twenty-four nonrandomized studies had a moderate risk of bias[30,32-49,51-54,56,58,59].

The three randomized studies reached evidence level 2[31,55,60]. All other studies reached evidence level 3 or 4.

Quality of the included studies using CHEC-scores was low. Scores range from 5.5 to 14.5 with a mean of 9.7. Low quality was mainly caused by insufficient information in the following domains: economic study design, time horizon, competing alternatives, perspective, ICER analysis, discounting, generalization and ethical issues.

3.3. Study results

Results of the studies are summarized in Additional File 5.2 in the appendix. Costs mentioned in studies ranged from implant costs to full hospital and societal perspective costs. Calculations of costs varied from costs, charges, or a combination of both. Due to heterogeneity between studies, we decided to mention cost ranges instead of means.

All studies mentioned healthcare perspective costs, ranging from $2,589 to $41,593 (costs) and from $34,255 to$49,535 (charges) for OTLIF and from $13,311 to $76,061 (costs) for MITLIF. Societal perspective costs ranged from $5,584 to $49,947 (costs) for OTLIF[29,31,33,36-39] and from $11,649 to $13,020 for MITLIF (costs)[37,38].

QALY gain for OTLIF was mentioned in ten studies[29,32,33,35-41]. Eight studies used EQ-5D to determine one-year mean QALY gain. This ranged from 0.100 to 0.440[29,32,33,36-39,41]. Two studies used SF-6D and found a one-year mean QALY gain of 0.057 and 0.079[32,40]. One study used SF-6D and reported a two-year QALY gain of 0.140[35].

QALY gain for MITLIF was mentioned in four studies[32,37,38,40]. Two studies determined one-year QALY gain using the EQ-5D (0.500 and 0.470)[37,38], one study used the SF-6D (0.113)[40] and one studies used both (EQ-5D 0.160, SF-6D 0.071)[32]. In all studies directly comparing OTLIF and MITLIF, QALY gain was higher in the MITLIF group[32,37,38,40].

Cost-effectiveness of OTLIF was mentioned in five studies, ranging from $47,303/QALY to $218,766/QALY[29,33,36,39,40]. Cost-effectiveness of MITLIF was mentioned in one study, $121,105/QALY[40]. One study directly comparing OTLIF and MITLIF showed comparable outcome in terms of QALY gain, and a non-significant trend of mean two-year savings of $9,637 in favor of MITLIF[37].

Four studies provided sufficient data to determine an incremental cost-effectiveness ratio (ICER)[32,37,38,40]. The ICER was estimated as (MITLIF Costs – OTLIF Costs) / (MITLIF QALY Gain – OTLIF QALY Gain). The results of the ICER estimations were -105.533[32], -107.077[37], -329.900[38], -123,235[40]. These negative ICERs suggest that MITLIF might be both

less costly and more effective than OTLIF. We included a diagram to visualize the ICER estimates of the individual studies (Figure 5.2.

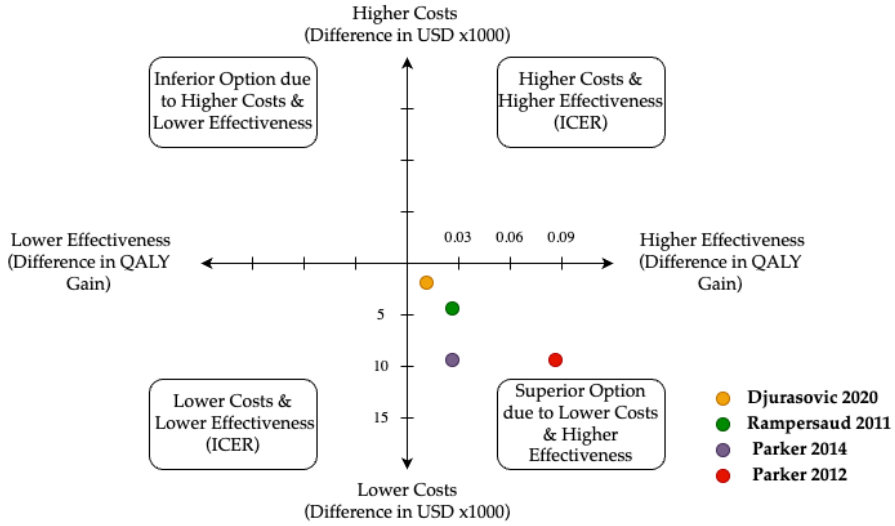

Figure 5.2 - Cost-effectiveness of MITLIF compared to OTLIF (ICER).

3.4. Meta-analysis

A meta-analysis was performed using healthcare perspective costs data of seven studies comparing OTLIF and MITLIF directly[32,37,38,40,51,53,56]. Two studies directly comparing both techniques were not included in the meta-analysis due to missing ranges or standard deviations[54,58].

The data table and forest plot can be found in Additional File 5.6 in the appendix. Study heterogeneity was low, with an $I^2$of 44% (P=0.10) for both Fixed and Random Effects analysis. The overall effect was in favor of MITLIF, with a significant mean difference of $2,650(95% CI [1.52, 3.78], P<0.001).

4. DISCUSSION

The aim of this systematic review and meta-analysis comparing costs and cost-effectiveness of OTLIF and MITLIF was to present an overview of the literature mentioning costs for OTLIF or MITLIF in patients with lumbar spondylolisthesis or lumbar degenerative disease. Furthermore, the methodological quality of the included studies was assessed and taken into account.

There was great heterogeneity in health care and societal perspective costs due to differences in calculation methods of costs, included costs, different in-, and exclusion factors and baseline characteristics. For example, four studies only included implant costs to determine healthcare perspective costs[46,48,49,60]. Due to variance in included cost data and cost calculations between studies, costs were reported in ranges instead of means. Healthcare perspective costs ranged from $2,589 to $49,535 for OTLIF and from $13,311 to $76,061 for MITLIF. Societal perspective costs ranged from $5,584 to $49,947 for OTLIF and from $11,649 to $13,020 for MITLIF. Cost-effectiveness of OTLIF ranged from $47,303/QALY to $218,766/QALY, cost-effectiveness of MITLIF, mentioned in only one study, was $121,105/QALY. Meta-analysis of hospital perspective costs from seven studies directly comparing OTLIF with MITLIF resulted in a mean difference of $2,650 (95% CI [1.52, 3.78], P<0.001). This indicates that the hospital perspective costs for MITLIF are significantly lower than OTLIF. Furthermore, none of the studies comparing OTLIF with MITLIF found that OTLIF was less expensive than MITLIF. We estimated an incremental cost-effectiveness ratio for four studies. In all four studies, costs associated with MITLIF were significantly lower. Furthermore, QALY gain based on EQ-5D was higher for MITLIF compared to OTLIF, although this difference was not statistically significant. The lower costs and higher QALY gain result in negative ICER estimates. This suggests that MITLIF might be a superior option when compared to OTLIF in terms of cost-effectiveness.

For the included studies, the overall risk of bias was high and quality using CHEC-list was low.

Combining all available information, we can state that the hospital perspective costs are relevantly lower for MITLIF compared with OTLIF. Studies directly comparing both techniques suggest this could be a consequence of lower transfusion rates due to lower blood loss, shorter duration of hospitalization, lower pharmacy and laboratory costs, lower implant costs and lower physical therapy costs associated with MITLIF compared to OTLIF[32,37,38,40,51,53,54,56,58]. There is no consensus concerning the operating room time for MITLIF compared to OTLIF[62], consequently, it is unclear to which extend the operating room time influences hospital perspective costs.

Furthermore, two studies directly comparing OTLIF and MITLIF including societal perspective costs found that these were lower in MITLIF[37,38]. These studies suggest that societal perspective costs are lower in MITLIF, mainly caused by lower absenteeism.

Comparison of the differences in QALY gain was difficult, as studies used different questionnaires to calculate QALY. Mean one-year QALY gain of OTLIF and MITLIF were comparable, ranging from 0.10 to 0.44 for OTLIF and from 0.16 to 0.50 for MITLIF. Although MITLIF seems to result in a slightly higher QALY gain, no studies directly comparing the effectiveness of OTLIF versus MITLIF found a statistically significant difference in QALY gain. Lower overall costs combined with comparable or slightly increased clinical outcomes could potentially lead to increased cost-effectiveness for MITLIF compared to OTLIF. For comparison; 2-year QALY gain (EQ-5D) is 0.25 ± 0.2

after total hip arthroplasty, 0.17 ± 0.19 after total knee arthroplasty and 0.16 ± 0.17 after unicompartmental knee arthroplasty[63].
The cost-effectiveness of MITLIF was mentioned in only one study; $121,105/QALY. The threshold for cost-effectiveness is subject to debate and may differ per country. The threshold of $50.000/QALY is mostly used in comparable economic evaluations. For OTLIF, two studies reported costs/QALY below this threshold[29,39], while all others, including the MITLIF study, reported costs/QALY well above this $50.000 threshold[33,36,40].
Our findings are in line with the findings of a review and meta-analysis published in 2015[62]. This review described a trend of reduction in perioperative costs for MITLIF compared with OTLIF. However, only six cost-effectiveness studies directly comparing the two techniques were included, resulting in a moderate heterogeneity in the meta-analysis of hospital costs (I^2=61%, P=0.04). All studies included in this review were likewise included in our review. Due to a broader search strategy and the availability of literature published after 2015, our review includes nine studies directly comparing OTLIF and MITLIF. Furthermore, the addition of two extra studies in the meta-analysis resulted in low heterogeneity. In order to include all valuable literature on costs, studies comparing OTLIF or MITLIF with other surgical techniques were also included. Thus, minimizing the possibility of missing relevant data.

As a result of the variety in reported data between studies, the only cost variable available and potentially interesting for meta-analysis was healthcare perspective costs reported in studies directly comparing OTLIF and MITLIF. Furthermore, comparison of the included studies was difficult due to variability in reporting and analyzing both health care and societal perspective costs. Compiled guidelines for economic evaluations of several countries are available. For instance, in the United States, the Panel on Cost-Effectiveness in Health and Medicine recommends performing cost-effectiveness studies from the societal perspective, which incorporates both direct (for instance health care costs) and indirect costs (for instance productivity losses)[64]. Nevertheless, only seven out of 32 studies reported on societal perspective costs. Definitions and sources differed between these studies, resulting in a broad cost range. For this reason, transferability of results to other countries, as well as comparison between studies, is challenging[65,66].

The review is also limited by several constraints. Our review and meta-analysis were limited to cost data. We did not individually analyze variables possibly affecting costs (e.g. blood loss, length of hospital stay, operating room time, missed working days, unpaid caregiver costs etc.). Likewise, we did not include studies concerning QALY without mentioning costs. This could lead to missing relevant data on difference in QALY gain.
Furthermore, we did not use the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) Checklist to evaluate the quality of each study individually[67]. This checklist evaluates the quality of the studies, focusing on the reporting of relevant items

in an economic evaluation study. We choose not to conduct individual assessments mainly due to the overall low quality of reporting in the included studies. Another limitation of this study was the inclusion of only full text, published studies and not conference proceedings, PhD dissertations or grey literature. This might have biased the results of the study. However, we believe that most eligible studies are included in this cost-effectiveness review.

The existing literature provided limited data on both societal and perspective costs and cost-effectiveness. Nonetheless, based on the assessment of the included studies, significant and clinically relevant differences were demonstrated concerning healthcare perspective costs and variables possibly affecting cost-effectiveness between OTLIF and MITLIF. However, more data are required from well-powered prospective randomized studies directly comparing the cost-effectiveness of OTLIF and MITLIF from both hospital and societal perspectives to obtain higher level of evidence. To improve the quality, transparency, and comparability of economic evaluations in lumbar spine surgery, we suggest that international guidelines on conducting and reporting economic evaluations would be beneficial. Recommendations for the conduct of economic evaluations are available for other medical specialties. An example of this is the recommendations for the conduct of economic evaluations in osteoporosis, in which a working group was convened by the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis to make recommendations for the design, conduct and reporting of economic evaluations in osteoporosis[68].

5. CONCLUSION

Results suggest that MITLIF might be more cost-effective than OTLIF, especially when comparing healthcare-related costs. However, both techniques are expensive when using a threshold of $50.000/QALY. Furthermore, it should be noted that the literature related to this topic is not of high quality and therefore these results should be interpreted with caution.

Both techniques are frequently used for patients with the same indication. When a surgical decision cannot be based on other important factors such as the surgeons experience, availability of the surgical technique, or surgical indication, cost-effectiveness should be an important factor in surgical decision-making. Prospective randomized studies directly comparing the cost-effectiveness of OTLIF and MITLIF from both hospital and societal perspectives are needed to obtain higher level of evidence. It is recommended that standardized measurement tools are used to determine quality of life, hospital perspective costs, and societal perspective costs to determine cost-effectiveness.

We suggest that international guidelines on conducting and reporting economic evaluations would be beneficial to improve the quality, transparency, and comparability of economic evaluations in lumbar spine surgery.

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APPENDIX FILE 5.1 MITLIF VS OTLIF SEARCH

Appendix: Search

PubMed 3 april 2020
#46 Search #16 AND #45
#45 Search #23 OR #26 OR #44 OR #35
#44 Search "Cost-Benefit Analysis"[Mesh]
#16 Search #15 AND #9
#35 Search Consumer Price Index[tiab] OR Consumer Price Indices[tiab] OR Consumption*[tiab] OR Cost*[tiab] OR Easterlin Hypothesis[tiab] OR Economic*[tiab] OR
Macroeconomic Factor*[tiab] OR Microeconomic Factor*[tiab] OR Production[tiab] OR Remittance*[tiab] OR Utility Theor*[tiab] OR Capital[tiab] OR Quality Adjusted Life Year*[tiab] OR
QALY[tiab] OR Healthy Years Equivalent*[tiab] OR price*[tiab] OR pricing[tiab]
#26 Search "Quality-Adjusted Life Years"[Mesh]
#23 Search "Economics"[Mesh]
#18 Search #17 AND #9
#17 Search tlif[tiab] OR “transforaminal lumbar interbody fusion”[tiab] OR mitlif[tiab]
#15 Search #12 OR #14
#14 Search Spinal Fusion*[tiab] OR Spondylodes*[tiab] OR Spondylosyndes*[tiab] OR spine fusion*[tiab] OR interbody fusion*[tiab] OR vertebral fusion*[tiab] OR vertebral condensation*[tiab] OR tlif[tiab] OR “transforaminal lumbar interbody fusion”[tiab] OR mitlif[tiab]
#12 Search "Spinal Fusion"[Mesh]
#9 Search #3 OR #8
#8 Search Spondylolisthes*[tiab] OR degenerat*[tiab] OR Spondylisthes*[tiab] OR slipped vertebra*[tiab] OR spondylolisthesis[tiab] OR spondylolisthesis[tiab] OR spondylolysthes*[tiab] OR vertebral sliding[tiab]
#3 Search "Spondylolisthesis"[Mesh] OR "Osteoarthritis, Spine"[Mesh]
- Filter: none
- Hits: 448

Cochrane:
- Search: ((Spondylolisthes* OR Spondylisthes* OR degenerat* OR slipped vertebra* OR spondylolisthesis OR spondylolisthesis OR spondylolysthes* OR vertebral sliding) OR (MesH
[spondylolisthesis]) OR (MeSH [osteoarthritis, Spine])) AND ((MeSH [Spinal Fusion]) OR Spinal Fusion*
OR Spondylodes* OR Spondylosyndes* OR spine fusion* OR interbody fusion* OR vertebral fusion*

OR vertebral condensation* OR tlif OR "transforaminal lumbar interbody fusion" OR mitlif) AND
(Consumer Price Index OR Consumer Price Indices OR Consumption* OR Cost* OR Easterlin
Hypothesis OR Economic* OR Macroeconomic Factor* OR Microeconomic Factor* OR Production OR
Remittance* OR Utility Theor* OR Capital OR Quality Adjusted Life Year* OR QALY OR Healthy Years
Equivalent* OR price* OR pricing OR (MeSH [Economics]) OR (MeSH [Quality-Adjusted Life Years]) OR
(MeSH [Cost-Benefit Analysis])
- Filter: Trials
- Hits: 210

Embase (OVID):
- Search:
#1 spine fusion.sh.
#2 (Spinal Fusion* or Spondylosyndes* or spine fusion* or vertebral fusion* or vertebral condensation* or tlif or transforaminal lumbar interbody fusion or mitlif).ab.
#3 economics.sh.
#4 quality adjusted life year.sh.
#5 cost benefit analysis.sh.
#6 1 or 2
#7 (Consumer Price Index or Consumer Price Indices or Consumption* or Cost* or Easterlin
Hypothesis or Economic* or Macroeconomic Factor* or Microeconomic Factor* or Production OR
Remittance* or Utility Theor* or Capital OR Quality Adjusted Life Year* or QALY OR Healthy Years
Equivalent* or price* or pricing).ab.
#8 3 or 4 or 5 or 6
#9 1 or 2
#10 (Spondylolisthes* or Spondylisthes* or degenerat* or slipped vertebra* or spondylolisthesis or
spondylolisthesis or spondylolysthes* or vertebral sliding).ab.
#11 intervertebral disk degeneration.sh.
#12 spondylolisthesis.sh.
#13 10 or 11 or 12
#14 8 and 9 and 13
- Filter: none
- Hits: 405

Cinahl (EBSCO):
- Search: MH spondylolisthesis OR MH spinal diseases OR AB (Spondylolisthes* OR Spondylisthes*
OR slipped vertebra* OR spondylo listhesis OR spondylo listhesis OR spondylolysthes* OR vertebral
sliding) AND MH spinal fusion OR AB (Spinal Fusion* OR Spondylodes* OR Spondylosyndes* OR
spine fusion* OR interbody fusion* OR vertebral fusion* OR vertebral condensation* OR tlif OR
"transforaminal lumbar interbody fusion" OR mitlif) AND (MH economics OR MH cost benefit
analysis OR MH quality adjusted life year) OR (Consumer Price Index OR Consumer Price Indices OR
Consumption* OR Cost* OR Easterlin Hypothesis OR Economic* OR Macroeconomic Factor* OR
Microeconomic Factor* OR Production OR Remittance* OR Utility Theor* OR Capital OR Quality
Adjusted Life Year* OR QALY OR Healthy Years Equivalent* OR price* OR pricing)
- Filter: none
- Hits: 211

ClinicalTrials.gov: http://clinicaltrials.gov/
- Search: Lumbar interbody fusion AND cost
- Filter: none
- Hits: 7

NHS Centre for Reviews and Dissemination (CRD): http://www.york.ac.uk/inst/crd/
- Search: Lumbar interbody fusion AND cost
- Filter: none
- Hits: 13

Web of science: https://apps.webofknowledge.com/
- Search:
((((((lumbar spondylolisthesis) OR lumbar instability) OR Spondylolisthesis OR degenerative))) AND
(((((TLIF) OR transforaminal lumbar interbody fusion)) OR ((MITLIF) OR minimally invasive lumbar
interbody fusion)) OR Spinal Fusion/methods)) AND (((((((cost) OR (Costs and Cost Analysis)) OR
(Cost-benefit analysis)) OR (economic evaluation)) OR (Pricing)) OR (cost-utility analysis)) OR (costeffectiveness
analysis)) OR (cost-effectiveness))

- Filter: none
- Hits: 127

Econlit:
- Search: ((((((lumbar spondylolisthesis) OR lumbar instability) OR "Spondylolisthesis"[Mesh] OR
degenerative OR "Osteoarthritis, Spine"[Mesh]))) AND (((((Transforaminal lumbar interbody fusion)
OR TLIF)) OR ((minimally invasive lumbar interbody fusion) OR MILIF)) OR "Spinal
Fusion/methods"[Mesh])) AND (((((((((cost) OR ("Costs and Cost Analysis"[Mesh])) OR ("Cost-Benefit
Analysis"[Mesh])) OR (economic evaluation)) OR (pricing))OR (cost-utility analysis)) OR (costeffectiveness
analysis)) OR (cost-effectiveness))
- Filter: none
- Hits: 5

Current Controlled Trials (CCT): http://controlled-trials.com/
- Search: Lumbar interbody fusion AND cost
- Filter: none
- Hits: 2

APPENDIX FILE 5.2 RESULTS OF INCLUDED STUDIES

Table S5.2 Results of included studies.

Author	Utility measurement tool	Cost resources		Charges or costs	QALY gain	Healthcare perspective Costs (US Dollars)	societal perspective costs (US Dollars)	Total costs (US Dollars)	Cost-utility score (US Dollars/ QALY)	QALY gain	Healthcare perspective Costs (US Dollars)	societal perspective costs (US Dollars)	Total costst (US Dollars)	Cost-Utility score (US Dollars/ QALY) & ICER
		Healthcare perspective	**Societal perspective**		**OTLIF**					**MITLIF**				
Adogwa et al. (2011)	EQ-5D	Medicare, DRG codes	Follow up of missed workdays and caregivers	Costs	EQ-5D: Mean gain 0.43, 2 years cumulative gain 0.86 CI 95% given	28,407 (surgery + outpatiant utilization)	13,031 (±12,783)	41,438 (±13,274)	48,210	-	-	-	-	-
Beckerman et al. (2019)	-	Hospital financial department	-	Costs		25,663	-	-	-	-	-	-	-	-
Chen et al. (2018)	-	Hospital financial department	-	Costs	-	11,451 (±1277)	-	-	-	-	-	-	-	-
Christensen et al. (2014)	SF-6D	National health insurance service register, DRG codes	DREAM database	Costs	-	35,436 CI 95% given	49,947 CI 95% given	85,383	-	-	-	-	-	-
Djurasovic et al. (2020)	EQ-5D, SF-6D	Hospital financial department	-	Costs	1 year: EQ-5D: 0.141 SF-6D: 0.057	16,950 (±3,903)	-	-	120,212	1 year: EQ-5D: 0.156 SF-6D: 0.071	15,367 (±3,574)	-	-	98,506

Table S5.2 (continued)

Author	Utility measurement tool	Cost resources		Charges or costs	QALY gain	Healthcare perspective Costs (US Dollars)	societal perspective costs (US Dollars)	Total costs (US Dollars)	Cost-utility score (US Dollars/ QALY)	QALY gain	Healthcare perspective Costs (US Dollars)	societal perspective costs (US Dollars)	Total costst (US Dollars)	Cost-Utility score (US Dollars/ QALY) & ICER
		Healthcare perspective	**Societal perspective**		**OTLIF**					**MITLIF**				
Eliades et al. (2015)	-	Hospital financial department	-	Costs	-	-	-	-	-	-	76,061CI 95% given	-	-	-
Feng et al. (2019)	-	Hospital finance department	-	Costs	-	-	-	-	-	-	19,978CI 95% given	-	-	-
Gandhoke et al. (2015)	EQ-5D	Hospital financial department	Follow up of missed workdays	Charges	EQ-5D: Mean gain 0.34, 2 years cumulative gain 0.67	34,383 CI 95% given	13,167 CI 95% given	46,420 CI 95% given	68,658CI 95% given	-	-	-	-	-
Garces et al.(2014)	-	Hospital financial department	-	Costs	-	-	-	-	-	-	28,196	-	-	-
Hartman et al. (2018)	-	Hospital financial department	-	Costs	-	-	-	-	-	-	28,784 range given	-	-	-
Jazini et al. (2018)	SF-6D estimated from ODI	Hospital financial department	-	Costs	SF-6D: 2 years cumulative gain 0.140	30,684 range given	-	-	219,171	-	-	-	-	-
Kelly et al. (2019)	-	Hospital financial department	-	Costs and charges	-	Implant costs: 12,194 (±1,650)	-	-	-	-	-	-	-	-

Table S5.2 (continued)

Author	Utility measurement tool	Cost resources		Charges or costs	QALY gain	Healthcare perspective Costs (US Dollars)	societal perspective costs (US Dollars)	Total costs (US Dollars)	Cost-utility score (US Dollars/ QALY)	QALY gain	Healthcare perspective Costs (US Dollars)	societal perspective costs (US Dollars)	Total costst (US Dollars)	Cost-Utility score (US Dollars/ QALY) & ICER
		Healthcare perspective	**Societal perspective**		**OTLIF**					**MITLIF**				
Khechen et al (2018)	-	Hospital financial department	-	Costs	-	-	-	-	-	-	20,485-21,181	-	-	-
Kim et al. (2017)	EQ-5D	Medicare, DRG codes, CPT codes	Follow up of missed workdays and caregivers	Costs and charges	EQ-5D 0.26 2 years cumulative gain 0.43	32,726 (±5,484)	5,584 (±7,217)	38,310 (±10,367)	89,093	-	-	-	-	-
Kotil et al. (2013)	-	Hospital financial department	-	Costs	-	Implant costs: 3,486	-	-	-	-	-	-	-	-
Omidi et al. (2018)	-	Hospital financial department	-	Costs	-	Implant costs: 2,589 (±427)	-	-	-	-	-	-	-	-
Parker et al. (2012)	EQ-5D	Medicare, DRG codes, Redbook	Follow up of missed workdays and homemaking days	Costs	EQ-5D Mean gain 0.41	29,011 range (27,174 – 30,847)	20,360 range given	49,371range given	120,417	EQ-5D 0.50	26,714 range (25,497 – 27,930)	13,020 range given	39,734 range given	79,468
Parker et al. (2014)	EQ-5D	Hospital financial department, Medicare, DRG codes,Redbook, CPT codes	Follow up of missed workdays,hom emaking days and caregivers	Costs	EQ-5D Mean gain 0.44, 2 years cumulative gain 0.70	30,281 (±6,292)	20,671 (±24,196)	50,952 (±21,450)	72,789	EQ-5D Mean gain 0.47, 2 years cumulative gain 0.77	29,406 (±6,502)	11,649 (±9,690)	41,055 (±11,279)	53,318

Table S5.2 (continued)

Author	Utility measurement tool	Cost resources		Charges or costs	QALY gain	Healthcare perspective Costs (US Dollars)	societal perspective costs (US Dollars)	Total costs (US Dollars)	Cost-utility score (US Dollars/ QALY)	QALY gain	Healthcare perspective Costs (US Dollars)	societal perspective costs (US Dollars)	Total costst (US Dollars)	Cost-Utility score (US Dollars/ QALY) & ICER
		Healthcare perspective	**Societal perspective**		**OTLIF**					**MITLIF**				
Parker et al. (Dec. 2012)	EQ-5D	Hospital financial department, Medicare, DRG codes, CPT codes	Follow up of missed workdays,hom emaking days and caregivers	Costs	EQ-5D Mean gain 0.43, 2 years cumulative gain 0.86	27,873	12,787 (±11,912)	40,660 (±13,025)	47,303 CI 95% given	-	-	-	-	-
Patel et al. (2008)	-	Hospital financial department	-	Charges	-	34,255	-	-	-	-	-	-	-	-
Pelton et al. (2012)	-	Hospital financial department	-	Costs	-	37,898 (total hosp. costs) 27,696 (direct) (±3,805)	-	-	-	-	33,779 (total hosp. costs) 22,683 (direct) (±6,191)	-	-	-
Rampersaud et al. (2011)	SF-6D	Hospital financial department	-	Costs	SF-6D 1 year: 0.079	17,501 (±5,821)	-	-	218,766	SF-6D 1 year: 0.113	13,311 (±3,071)	-	-	121,105
Ren et al. (2019)	-	Hospital financial department	-	Costs	-	-	-	-	-	-	19,604 (±860)	-	-	-
Singh et al. (2014)	-	Hospital financial department	-	Costs and charges	-	27,047 (±4,021)	-	-	-	-	22,409 (±5,591)	-	-	-

Table S5.2 (continued)

Author	Utility measurement tool	Cost resources		Charges or costs	QALY gain	Healthcare perspective Costs (US Dollars)	societal perspective costs (US Dollars)	Total costs (US Dollars)	Cost-utility score (US Dollars/ QALY)	QALY gain	Healthcare perspective Costs (US Dollars)	societal perspective costs (US Dollars)	Total costst (US Dollars)	Cost-Utility score (US Dollars/ QALY) & ICER
		Healthcare perspective	**Societal perspective**		**OTLIF**						**MITLIF**			
Sulaiman et al. (2014)	-	Hospital financial department	-	Costs	-	41,593	-	-	-	-	21,081	-	-	-
Tian et al. (2016)	-	Hospital financial department	-	Costs	-	-	-	-	-	-	19,756 (±3,343)	-	-	-
Tye et al. (2018)	EQ-5D	Hospital financial department	-	Costs and charges	EQ-5D Mean gain 0.10	8,628 Range given	-	-	-	-	-	-	-	-
Ver et al. (2020)	-	Hospital financial department	-	Costs	-	17,520 (±6,097)	-	-	-	-	15,923 (±2,913)	-	-	-
Whitecloud et al. (2001)	-	Hospital financial department	-	Charges	-	49,535	-	-	-	-	-	-	-	-
Wong et al (2014)	-	Hospital financial department	-	Costs	-	27,488	-	-	-	-	23,327	-	-	-
Wu et al. (2020)	-	Hospital financial department	-	Costs	-	16,025 (±1,280)	-	-	-	-	-	-	-	-
Xue et al. (2012)	-	Hospital financial department	-	Costs	-	Implant costs: 5,220 (±23)	-	-	-	-	-	-	-	-

Abbreviations: CPT codes = Current Procedural Terminology codes, DRG codes= Diagnosis Related Group codes, EQ-5D = EuroQol-five Dimensions, MITLIF = Minimally Invasive Transforaminal Lumbar Interbody Fusion, ODI = Oswestry Disability Index, OTLIF = Open Transforaminal Lumbar Interbody Fusion, QALY = Quality Adjusted Life Years, SF-6D = Short Form-six Dimensions.

For comparison, all costs were converted to American Dollars with reference year 2018.

APPENDIX FILE 5.3 STUDY CHARACTERISTICS

Table S5.3 Study characteristics of included studies.

Author	Country of origin	Design	Study Design	Follow-up time	Number of patients			Mean age (in year)	Indication for surgery	Level of surgery	Level of evidence	CHEC-list score
						O TLIF	*MI TLIF*					
Adogwa et al. (2011)	USA	Cost-effectiveness study	Prospective cohort study	2 years	45	45	-	51.0	Spondylolisthesis	1-lvl	3	11.5
Beckerman et al. (2019)	USA	Cost-effectiveness study	Retrospective comparative cohort study	2 years	532	-	258	55.0	Spondylolisthesis, degenerative disc disease, deformity, trauma	1-lvl	4	9.0
Chen et al. (2018)	China	Financial analysis	Retrospective comparative cohort study	2 years	63	34	-	51.0	Degenerative disc disease	1-lvl	4	8.0
Christensen et al. (2014)	Denmark	Cost-effectiveness study	Randomized controlled trial	2 years	100	51	-	51.0	Long lasting back-pain (including spondylolisthesis)	-	2	14.5
Djurasovic et al. (2020)	USA	Cost-effectiveness study	Prospective comparative cohort study	1 year	66	33	33	57.3	Spondylolisthesis, degenerative disc disease	1- or 2-lvl	3	11.0
Eliades et al. (2015)	USA	Financial analysis	Retrospective comparative cohort study	2 year	24	-	10	62.5	Spondylolisthesis, degenerative disc disease	1-lvl	4	6.5

Table S5.3 (continued)

Author	Country of origin	Design	Study Design	Follow-up time	Number of patients		Mean age (in year)	Indication for surgery	Level of surgery	Level of evidence	CHEC-list score
					O TLIF	*MI TLIF*					
Feng et al. (2019)	China	Financial analysis	Retrospective comparative cohort study	30 days post-discharge	74	-	30	59.0	Spondylolisthesis, degenerative disc disease, spinal stenosis	1-lvl	4	5.5
Gandhoke et al. (2015)	USA	Cost-effectiveness study	Prospective comparative cohort study	2 years	74	45	-	57.6	Spondylolisthesis, failed back syndrome, etc.	1-level	3	13.5
Garces et al. (2014)	USA	Financial analysis	Retrospective comparative cohort study	1 year	112	-	39	62.8	Spondylolisthesis, degenerative disc disease, spondylosis, HNP	1- or 2-lvl	4	9.0
Hartman et al. (2018)	USA	Cost-effectiveness study	Retrospective comparative cohort study	30 days post-discharge	20	-	10	56.9	Unclear (Similar pathology)	1-lvl	4	8.0
Jazini et al. (2018)	USA	Cost-effectiveness study	Retrospective comparative cohort study	2 years	62	31	-	54.8	Spondylolisthesis	1-level	4	10.5
Kelly et al. (2019)	USA	Financial analysis	Retrospective comparative cohort study	2 years	119	70	-	65.0	Spondylolisthesis	1-lvl	4	8.0
Khechen et al. (2018)	USA	Financial analysis	Retrospective cohort study	During hospitalization	298	-	298	53.4	Degenerative pathology	1-lvl	4	8.0

Table S5.3 (continued)

Author	Country of origin	Design	Study Design	Follow-up time	Number of patients			Mean age (in year)	Indication for surgery	Level of surgery	Level of evidence	CHEC-list score
						O TLIF	*MI TLIF*					
Kim et al. (2017)	USA	Cost-effectiveness study	Retrospective comparative cohort study	2 years	99	62	-	58.7	Spondylolisthesis	1-lvl	4	12.0
Kotil et al. (2013)	Turkey	Financial analysis	Prospective comparative cohort study	2 years	60	30	-	48.9	Foraminal disc herniation, spinal stenosis, degenerative disc disease	1-lvl	3	8.0
Omidi-Kashani et al. (2018)	Iran	Financial analysis	Retrospective comparative cohort study	2 years	60	30	-	48.9	Spondylolisthesis	1-lvl	4	8.0
Parker et al. (2012)	USA	Cost-effectiveness study	Prospective comparative cohort study	2 years	30	15	15	50.3	Spondylolisthesis	1-lvl	3	14.5
Parker et al. (2014)	USA	Cost-effectiveness study	Prospective comparative cohort study	2 years	100	50	50	53.1	Spondylolisthesis	1-lvl	3	14.5
Parker et al. (2012 December)	USA	Cost-effectiveness study	Prospective cohort study	2 years	45	45	-	50.9	Spondylolisthesis	1-lvl	3	11.5
Patel et al. (2008)	USA	Financial analysis	Retrospective comparative cohort study	During hospitalization	40	10	-	-	Unclear	1-lvl	4	8.0

Table S5.3 (continued)

Author	Country of origin	Design	Study Design	Follow-up time	Number of patients			Mean age (in year)	Indication for surgery	Level of surgery	Level of evidence	CHEC-list score
						O TLIF	*MI TLIF*					
Pelton et al. (2012)	USA	Financial analysis	Prospective comparative cohort study	6 months	66	33	33	50.8	Spondylolisthesis, degenerative disc disease	1-lvl	3	12.0
Rampersaud et al. (2011)	Canada	Cost-effectiveness study	Retrospective comparative cohort study	1 year	78	41	37	56.1	Spondylolisthesis	1- or 2-lvl	4	14.0
Ren et al. (2019)	China	Financial analysis	Retrospective comparative cohort study	1 year	74	-	31	63.9	Far lateral disc herniation	1-lvl	4	8.0
Singh et al. (2014)	USA	Financial analysis	Retrospective comparative cohort study	60 days	66	33	33	50.8	Spondylolisthesis, degenerative disc disease, spinal stenosis	1-lvl	4	11.5
Sulaiman et al. (2014)	USA	Financial analysis	Prospective comparative cohort study	2 years	68	11	57	60.3	Spondylolisthesis	All lvls	3	10.0
Tian et al. (2016)	China	Financial analysis	Randomized controlled trial	2 years	97	-	47	57.2	Degenerative disease	1-lvl	2	10.0
Tye et al. (2018)	USA	Cost-effectiveness study	Retrospective comparative cohort study	1 year	66	25	-	52.4	Spondylolisthesis	1-lvl	4	9.5

Table S5.3 (continued)

Author	Country of origin	Design	Study Design	Follow-up time	Number of patients			Mean age (in year)	Indication for surgery	Level of surgery	Level of evidence	CHEC-list score
						O TLIF	*MI TLIF*					
Ver et al. (2020)	USA	Financial analysis	Retrospective comparative cohort study	During hospitalization	156	52	52	53.8	Spondylolisthesis, stenosis, degenerative disease	1- or 2-lvl	4	6.5
Whitecloud et al. (2001)	USA	Financial analysis	Retrospective comparative cohort study	1 year	80	40	-	44.7	Spondylolisthesis, degenerative disc disease, failed back syndrome	1-level	4	5.5
Wong et al. (2014)	USA	Financial analysis	Prospective comparative cohort study	4 years	68	34	34	60.2	Spondylolisthesis, lumbar instability, degenerative disc disease	1- lvl	3	8.0
Wu et al. (2020)	China	Financial analysis	Retrospective comparative cohort study	1 year	44	24	-	53.5	Degenerative disc disease, spinal stenosis	1-lvl	4	7.0
Xue et al. (2012)	China	Financial analysis	Randomized controlled trial	1.5 years	80	43	-	58.2	Degenerative disease	1- or 2-lvl	2	9.5

Abbreviations: CHEC-list = Consensus Health Economic Criteria-list, Lvl = level, MITLIF = Minimally Invasive Transforaminal Lumbar Interbody Fusion, OTLIF = Open Transforaminal Lumbar Interbody Fusion

APPENDIX FILE 5.4 RISK OF BIAS

Table S5.4 Risk of bias assessed with the bias assessment tool of the Cochrane Handbook for Systematic Reviews of Interventions.

Author	Design	Date collection	Selection bias	Performance bias	Detection bias	Attrition bias	Reporting bias	Other bias	Conclusion
Christensen et al. (2013)	Cost-effectiveness study	Randomized controlled trial	-	🔴	🔴	🟢	-	None	🔴
Tian et al. (2016)	Financial analysis	Randomized controlled trial	-	🔴	🔴	🟢	🟢	None	🔴
Xue et al. (2012)	Financial analysis	Randomized controlled trial	-	🔴	🔴	🟢	-	None	🔴

Author	Study design	Bias due to confounding	Bias in selecting patients	Bias in classification of interventions	Bias due to deviation from intended intervention	Bias due to missing data	Bias in measure outcome	Bias in selection of the reported results	Other bias	Conclusion
Adogwa et al. (2011)	Prospective cohort study	🔴	🟢	🟡	🟢	🟢	🟡	🔴	None	🔴
Djurasovic et al. (2020)	Prospective comparative cohort study	🟢	🟡	🟢	🟢	🟢	🟡	🟢	🟡	🟡
Gandhoke et al. (2015)	Prospective comparative cohort study	🟡	🟡	🟢	🟡	🟢	🟡	🟢	None	🟡
Kotil et al. (2013)	Prospective comparative cohort study	🟡	🟢	🟢	🟡	🟢	🟡	🟢	None	🟡
Parker et al. (2012)	Prospective comparative cohort study	🟢	🟢	🟢	🟢	🟢	🟡	🟢	None	🟡
Parker et al. (2014)	Prospective comparative cohort study	🟢	🟢	🟢	🟢	🟢	🟡	🟢	None	🟡

Table S5.4 (continued)

Author	Study design	Bias due to confounding	Bias in selecting patients	Bias in classification of interventions	Bias due to deviation from intended intervention	Bias due to missing data	Bias in measure outcome	Bias in selection of the reported results	Other bias	Conclusion
Parker et al. (Dec. 2012)	Prospective cohort study	🔴	🟢	🟡	🟢	🟢	🟡	🟢	None	🟡
Pelton et al. (2012)	Prospective comparative cohort study	🟢	🟢	🟢	🟡	🟢	🟡	🟢	None	🟡
Sulaiman et al. (2014)	Prospective comparative cohort study	🟡	🟢	🟢	🟢	🟢	🟡	🟢	None	🟡
Wong et al (2014)	Prospective comparative cohort study	🟡	🟡	🟢	🟡	🟡	🟡	🟢	None	🟡
Beckerman et al. (2019)	Retrospective comparative cohort study	🔴	🟡	🟢	🟢	🟡	🟡	🟢	None	🟡
Chen et al. (2018)	Retrospective comparative cohort study	🟡	🟡	🟢	🟢	🟢	🟡	🟢	None	🟡
Eliades et al. (2015)	Retrospective comparative cohort study	🟢	🟡	🟢	🟢	🔴	🟡	🟢	None	🟡
Feng et al. (2019)	Retrospective comparative cohort study	🟢	🟢	🟢	🟢	🟡	🟡	🟢	None	🟡
Garces et al. (2014)	Retrospective comparative cohort study	🔴	🟡	🟢	🟢	🟢	🟡	🟢	None	🟡
Hartman et al. (2018)	Retrospective comparative cohort study	🟡	🟢	🟢	🟢	🟡	🟡	🟢	🔴	🟡

Table S5.4 (continued)

Author	Study design	Bias due to confounding	Bias in selecting patients	Bias in classification of interventions	Bias due to deviation from intended intervention	Bias due to missing data	Bias in measure outcome	Bias in selection of the reported results	Other bias	Conclusion
Jazini et al. (2018)	Retrospective comparative cohort study	🟢	🟡	🟢	🟢	🟢	🟡	🟢	None	🟡
Kelly et al. (2019)	Retrospective comparative cohort study	🟢	🟡	🟢	🟢	🟡	🟡	🟢	None	🟡
Khechen et al. (2018)	Retrospective comparative cohort study	🟢	🟡	🟢	🟢	🟢	🟡	🟢	None	🟡
Kim et al. (2017)	Retrospective comparative cohort study	🟡	🟡	🟢	🟢	🟢	🟡	🟢	None	🟡
Omidi-Kashani et al. (2018)	Retrospective comparative cohort study	🟡	🟡	🟢	🟢	🟢	🟡	🟢	None	🟡
Patel et al. (2008)	Retrospective comparative cohort study	🔴	🔴	🟢	🟢	🟡	🟡	🔴	None	🔴
Rampersaud et al. (2011)	Retrospective comparative cohort study	🟡	🟢	🟢	🟢	🟡	🟡	🟢	None	🟡
Ren et al. (2019)	Retrospective comparative cohort study	🟢	🟡	🟢	🟢	🟡	🟡	🟢	None	🟡
Singh et al. (2014)	Retrospective comparative cohort study	🟢	🟡	🟢	🟢	🟡	🟡	🟢	None	🟡
Tye et al. (2018)	Retrospective comparative cohort study	🟢	🟡	🟡	🟢	🟢	🟡	🟢	🟡	🟡

Table S5.4 (continued)

Author	Study design	Bias due to confounding	Bias in selecting patients	Bias in classification of interventions	Bias due to deviation from intended intervention	Bias due to missing data	Bias in measure outcome	Bias in selection of the reported results	Other bias	Conclusion
Ver et al. (2020)	Retrospective comparative cohort study	●	●	●	●	●	●	●	●	●
Whiteclou d et al. (2001)	Retrospective comparative cohort study	●	●	●	●	●	●	●	●	●
Wu et al. (2020)	Retrospective comparative cohort study	●	●	●	●	●	●	●	None	●

Grading System: ● Serious ● Moderate ● Low. Scale: Low, moderate, serious, unclear.

APPENDIX FILE 5.5 METHODOLOGICAL QUALITY OF ECONOMICAL EVALUATIONS (CHEC-LIST)

Table S5.5 Methodological quality of included studies assessed with the Consensus Health Economic Criteria (CHEC) list.

Article	1. Describes study population	2. Competing alternatives	3. Research question	4. Economic study design	5. Time horizon	6. Perspective	7. Relevant costs	8. Appropriately measured costs	9. Appropriately valued costs	10. Relevant outcomes	11.Appropriately measured outcomes	12. Appropriately valued outcome	13. ICER	14. Discounted	15. Sensitivity analyses	16. Correct conclusions	17. Generalization	18. Conflict of interest	19. Ethical issues	Total
Adogwa et al. (2011)	+	-	+	-	+	+	+	+	+/-	+	+	+	-	-	-	+	-	+	-	11.5
Beckerman et al. (2019)	+	-	+	-	-	-	+	+	-	+	+	-	-	-	-	+	+	+	-	9.0
Chen et al. (2018)	+	-	+	-	-	-	-	+	-	+	+	+	-	-	-	+	-	+	-	8.0
Christensen et al. (2014)	+	-	+	+	+	+	+/-	+/-	+/-	+	+/-	+	+	+/-	+	+	+	+	-	14.5
Djurasovic et al. (2020)	+	+	+	+	+	-	-	+	-	+	+	+	-	-	-	+	+/-	+/-	-	11.0
Eliades et al. (2015)	+	+	+	-	-	-	-	-	-	+	+	+	-	-	-	+/-	-	-	-	6.5
Feng et al. (2019)	+	-	+	-	-	-	-	-	-	+	-	-	-	-	-	+/-	+	+	-	5.5
Gandhokete al. (2015)	+/-	-	+	+	+	+	+/-	+	-	+	+	+	+	-	+/-	+	+	+	-	13.5
Garces et al.(2014)	+/-	-	+	+	+	-	-	+	-	+	+/-	-	-	-	-	+	+	+	-	9.0
Hartman et al. (2018)	+	+/-	+	+	+	-	-	-	-	+	+	-	-	-	-	+	-	+/-	-	8.0
Jazini et al. (2018)	+	+	+	+	+	-	+/-	-	-	+	+/-	+	+	-	-	+	-	+/-	-	10.5

Table S5.5 (continued)

Article	1. Describes study population	2. Competing alternatives	3. Research question	4. Economic study design	5. Time horizon	6. Perspective	7. Relevant costs	8. Appropriately measured costs	9. Appropriately valued costs	10. Relevant outcomes	11.Appropriately measured outcomes	12. Appropriately valued outcome	13. ICER	14. Discounted	15. Sensitivity analyses	16. Correct conclusions	17. Generalization	18. Conflict of interest	19. Ethical issues	Total
Kelly et al. (2019)	+	+	+/-	-	-	-	+/-	-	-	+	+	+	-	-	-	+	-	+	-	8.0
Khechen et al (2018)	+	-	+	-	-	-	-	-	-	+	+	-	-	-	-	+	+/-	+	-	8.0
Kim et al. (2017)	+	+/-	+	+	+	+	+	+	-	+	+	+	-	-	-	+/-	-	+	-	12.0
Kotil et al. (2013)	+	+	+	-	-	-	-	-	-	+	+	+	+	-	-	+	-	+	-	8.0
Omidi et al. (2018)	+	+	+	-	-	-	-	-	-	+	+	+	-	-	-	+	-	+	-	8.0
Parker et al. (2012)	+	+	+	+	+	+	+	+	+/-	+	+	+	+	-	-	+	-	+	-	14.5
Parker et al. (2014)	+	+	+	+	+	+	+	+	+/-	+	+	+	+	-	-	+	-	+	-	14.5
Parker et al. (Dec. 2012)	+/-	-	+	+	+	+	+	+	-	+	+	+	-	-	-	+	-	+	-	11.5
Patel et al. (2008)	-	+	+	-	+	-	-	+	-	+	+	-	-	-	-	+	-	+	-	8.0
Pelton et al. (2012)	+	+	+	+	+	-	-	+	-	+	+	+	-	-	-	+	+	+	-	12.0

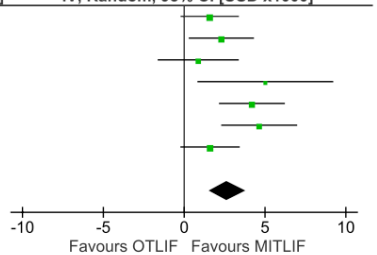
Table S5.5 (continued)

Article	1. Describes study population	2. Competing alternatives	3. Research question	4. Economic study design	5. Time horizon	6. Perspective	7. Relevant costs	8. Appropriately measured costs	9. Appropriately valued costs	10. Relevant outcomes	11.Appropriately measured outcomes	12. Appropriately valued outcome	13. ICER	14. Discounted	15. Sensitivity analyses	16. Correct conclusions	17. Generalization	18. Conflict of interest	19. Ethical issues	Total
Rampersaud et al. (2011)	+	+	+	+	+	+	+/-	+	-	+	+	+	-	+/-	-	+	+	+	-	14.0
Ren et al. (2019)	+	+	-	-	+	-	-	-	-	+	+	+	-	-	-	+	+/-	+/-	-	8.0
Singh et al. (2014)	+	+	+	-	+	-	+	+/-	-	+	+	+	-	-	-	+	+	+	-	11.5
Sulaiman et al. (2014)	+	+	+	+/-	+	-	+/-	+/-	+/-	-	+	+	-	-	-	+	-	+	-	10.0
Tian et al. (2016)	+	+	+	-	+	-	-	-	-	+	+	+	-	-	-	+	+	+	-	10.0
Tye et al. (2018)	+	-	+/-	+	+	-	+/-	+/-	-	+	+	+	-	+	-	+/-	-	+/-	-	9.5
Ver et al. (2020)	+	+	+	-	-	-	-	+/-	-	+/-	+	-	-	-	-	+	+/-	-	-	6.5
Whitecloud et al. (2001)	+	+	+	-	+/-	-	-	+/-	-	+/-	+	-	-	-	-	-	-	-	-	5.5
Wong et al (2014)	+	+	-	-	+	-	-	-	-	+	+	+	-	-	-	+	-	+	-	8.0
Wu et al. (2020)	+	+	-	-	+/-	-	-	-	-	+	+	+	-	-	-	+/-	-	+	-	7.0
Xue et al. (2012)	+	+	+	-	+	-	-	-	-	+	+	+	-	-	-	+	-	+	-	9.5

APPENDIX FILE 5.6 DATA TABLE & FOREST PLOT

	OTLIF			MITLIF				Mean Difference	Mean Difference
Study or Subgroup	Mean [USD x1000]	SD [USD x1000]	Total	Mean [USD x1000]	SD [USD x1000]	Total	Weight	IV, Random, 95% CI [USD x1000]	IV, Random, 95% CI [USD x1000]
Djurasovic 2020	16.95	3.9	33	15.37	3.57	33	18.0%	1.58 [-0.22, 3.38]	
Parker 2012	29.01	3.32	15	26.71	2.2	15	16.2%	2.30 [0.28, 4.32]	
Parker 2014	30.28	6.29	50	29.41	6.5	50	12.6%	0.87 [-1.64, 3.38]	
Pelton 2012	27.7	3.81	13	22.68	6.19	11	5.9%	5.02 [0.82, 9.22]	
Rampersaud 2011	17.5	5.82	41	13.31	3.07	37	16.0%	4.19 [2.15, 6.23]	
Singh 2014	27.05	4.02	33	22.41	5.59	33	13.6%	4.64 [2.29, 6.99]	
Ver 2020	17.52	6.1	52	15.92	2.91	52	17.7%	1.60 [-0.24, 3.44]	
Total (95% CI)			**237**			**231**	**100.0%**	**2.65 [1.52, 3.78]**	

Heterogeneity: Tau² = 1.00; Chi² = 10.78, df = 6 (P = 0.10); I² = 44%
Test for overall effect: Z = 4.59 (P < 0.00001)



PART III

ECONOMIC EVALUATIONS IN SPINE SURGERY

CHAPTER 6

EVIDENCE-BASED RECOMMENDATIONS FOR ECONOMIC EVALUATIONS IN SPINE SURGERY: STUDY PROTOCOL FOR A DELPHI CONSENSUS

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ABSTRACT

Introduction
Considering the rising global healthcare expenses, economic evaluations are more important than ever. Even though the number of studies regarding costs and cost-effectiveness is increasing, the quality of these studies remains relatively low. This is mainly caused by abundant heterogeneity in methods used for determining, calculating and reporting cost data, despite current general guidelines for the conduct of economic evaluations. Disease-specific recommendations for the conduct of economic evaluations in the field of spine surgery, as complement to existing general guidelines, will ameliorate overall research quality, comparability, and interpretability and thus, the overall quality. We aim to provide expert-based recommendations for the design, conduct, and reporting of economic evaluations in spine surgery.

Methods and analysis
A modified Delphi study will be conducted to formulate expert-based recommendations. The following steps will be taken:
1. The conduct of a systematic review to identify relevant publications and identify relevant authors. Formation of an expert group and a Delphi-panel.
2. Drafting of statements based on articles included in the systematic literature review. Validation of drafted statements by the expert group.

Step 2 can be repeated up to 3 times, statements can be discarded and adjusted in these rounds. Statements with more than 75% agreement will be accepted as consensus statements.
3. Validation of statements by the Delphi-panel.
4. Final recommendations.

Ethics and dissemination
The final recommendations are intended for (clinical) researchers in the field of cost-effectiveness in spine surgery. The Delphi method ensures that the final output reflects the opinions of international participants and gives insight in the adherence level to the recommendations. The aim is to reach uniformity in design, conduct and reporting of these studies, as is currently lacking. This will provide a solid basis to determine cost-effectiveness of spine surgeries and consequently aid to limit the rising healthcare costs.

Strengths and limitations of this study
- The multidisciplinary expert group and Delphi Panel in this proposed study are formed by selecting authors from relevant publications identified by a systematic review, resulting in a representative panel with limited selection bias.
- The level of agreement to reach consensus and the maximum number of Delphi rounds are predefined to avoid bias in reaching consensus.
- A potential bias may occur as not all members invited will agree to participate.
- In case of live voting at a congress, results may be biased by the specific interest area of the congress, attendance of the voting cohort and presentation of the recommendations.
- The expert meeting may limit thorough discussion of complex problems because of time limits and large-group discussion.

1. INTRODUCTION

Economic evaluations are increasingly important considering the growing healthcare expenses. The number of people aged 60 years or older is expected to double by 2050[1]. As older individuals are more likely to require spine surgery, the amount of spine surgeries is also expected to increase. This, in turn, will result in higher healthcare-related costs[2–4]. To limit the increase of spine surgery-related healthcare costs, scarce healthcare resources should be allocated efficiently. Therefore, the most cost-effective surgical technique should be identified and implemented[5,6].

The value of economic evaluations is progressively renowned, as reflected by the observed increase in studies mentioning costs and cost-effectiveness in the last decade[5–7]. However, the variable quality and reporting of these economic evaluations limits their comparability and usefulness. This is mainly a result of heterogeneity in study design, study data, and assumptions. An important factor for instance, is the heterogeneity in determining, calculating and reporting cost data[8]. Current outcomes of economic evaluations in spine-surgery vary largely in healthcare perspective and societal perspective costs due to differences in calculation methods of costs and/or charges, included costs, different in- and exclusion criteria and baseline characteristics[9,10]. The Panel on Cost-Effectiveness in Health and Medicine in the United States recommends performing cost-effectiveness studies from both the healthcare and the societal perspective[11]. Nevertheless only a minority of economic evaluations report on societal perspective costs[12].

General guidelines and recommendations regarding the proper conduct of economic evaluations are available, including the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist, the series of Modelling Good Research Practices published by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) and the recommendations for Conduct, Methodological Practices, and Reporting of Cost-effectiveness Analyses from the Second Panel on Cost-Effectiveness in Health and Medicine[7,11,13]. A limitation of these general guidelines is that by their nature they do not incorporate disease- and topic-specific recommendations. As suggested by Carias et al.: "it is not practical to adopt a single set of criteria for all public health CEAs; one size does not fit all"[14]. Compared and in supplement to the generally accepted methodologic standards, it would thus be beneficial to have disease-specific guidelines to provide additional recommendations. For instance, this has been done for osteoporosis. Only a few disease-specific guidelines regarding the conduct of economic evaluations are available, however, and not in the field of spine surgery[15–18].

Kepler et al. reviewed the existing economic evidence in spine surgery in 2012[19]. This study portrays the lack of homogenous reporting in terms of study design, study population, pathology studied, cost calculations and utility used. Moreover, they observed that only 12% of studies adhered to the recommendations of the US Second Panel of Cost-effectiveness in Health and Medicine. Subsequently, the lack of standardized costing methodology in spine surgery research is also extensively described

by Alvin et al.[8]. The lack of several key aspects in cost calculations are described. First of all, the perspective of included costs should be considered. Secondly, the acquisition and definition of costs should be considered. Payments, charges, costs and expected reimbursements are separate entities that should not be used synonymously. Currently, there is an important difference in the (combined) use of Medicare reimbursements, case-costing databases, cost-to-charge ratios and national costing databases. Finally, the accurate calculation of costs is the timeframe in which costs are measured should be considered. Moreover, the need for appropriate discounting, and consideration of inflation and country is emphasized. They suggest future research could consider to include Net Monetary Benefit (NMB) and/or Time-based activity-based costing (TDABC) to overcome several limitations in current cost-effectiveness[8].
More recently, Radcliff et al. and Droeghaag et al. both described the current literature concerning cost-effectiveness research in cervical spine surgery and lumbar spine surgery respectively[9,10].
In both studies, the authors note that absence of uniformity in existing literature is apparent.
The aim of a disease-specific guideline, is not only to suggest optimal costing methods and utility measurements, but to incorporate specific disease related components to these general recommendations."

The lack of homogeneity in economic evaluations regarding spine surgery impedes proper interpretation by healthcare professionals and financial decision-makers. Recommendations to conduct economic evaluations in this field, as a complement to the existing general guidelines, should ameliorate overall research quality, comparability and interpretability.
Therefore, this study has four objectives; (1) To create disease-specific recommendations for the design and conduct of economic-evaluations in spine surgery, (2) To construct recommendations for reporting of economic evaluations in spine-surgery as a complement to the CHEERS checklist, (3) To define a disease-specific reference as a minimum standard for all economic analyses in spine-surgery in order to reduce inter-study heterogeneity, (4) To discuss methodologic challenges and defining the need for future research.

2. METHODS

This study will be conducted according to the RAND/UCLA Appropriateness Method, a modified Delphi Process[20,21]. A four-step process will be followed to create and validate disease-specific statements and recommendations for the conduct and reporting of economic evaluations in spine surgery.

The authors will form a multi-center research group which will consist of a working group and an advisory board. The working group will consist of researchers that are in charge of conduct of the study (n=5). The advisory panel (between 5 and 10) will consist of experienced researchers, both clinical (neurosurgeons, orthopedic surgeons, clinical researchers e.g.) and health-economic experts. The role of the advisory board is to advise and supervise the conceptualization of the study, the first drafts of the statements and the conduct of the study.

2.1. Systematic literature review

A systematic review is conducted in July 2021 to assess articles concerning general guidelines or recommendations on economic evaluations, or articles concerning economic evolutions in spine surgery. The systematic review is conducted in accordance with the PRISMA statement[22,23]. The literature search is conducted using several terms, including, but not limited to: "economic evaluation", "cost-effectiveness" and "spine surgery". The full search strategy can be found in Appendix File A. The following databases will be searched: PubMed, Web of Science, Embase, Cochrane, CINAHL, EconLit, NHS-EED.

2.1.1. Identifying relevant studies

Relevant studies will be selected and reviewed based on titles and abstracts. Articles deemed appropriate for inclusion will be reviewed for further analysis. Reviews concerning economic evaluations in spine-surgery, published economic evaluations in spine-surgery, general guidelines for the conduct of economic evaluations and disease-specific guidelines for economic evaluations will be included. Included articles will be cross-referenced. Studies will be selected by two independent reviewers. Duplicates will be removed, potentially eligible studies will be screened on title and abstract, and full texts will be assessed using abovementioned eligibility criteria. Level of evidence will be assessed for all relevant studies. Discrepancies between reviewers will be resolved through discussion and with the assistance of a third reviewer if needed.

2.1.2. Identifying relevant authors and expert group formation

First and last authors will be identified in included articles deriving from the systematic literature search to form the expert panel. This will include those who are most active in publishing, but it may also exclude some of the experts in the field. To prevent this, the first and last identified authors will be asked to consider whether one of their co-authors might be a more suitable candidate, after which the recommended co-author may be included in the expert panel.

The expert group should at least include scientists of the following disciplines: neurosurgery, orthopedic surgery and health-economics.

In addition, economic experts will be selected from general guidelines and disease-specific guidelines (N=5) by evaluating the number of publications and citations. Clinical experts will be selected from economic evaluations in spine surgery (N=10). Together

with the advisory board of the research group they will form the expert group. The role of the expert group will be to perform a primary validation of statements drafted by the research group. This step is essential to assess external (i.e., international) validity of statements drafted by the research group, before approaching a larger group for validation. Finally, members of the research group can also propose potential experts.
All experts will be approached for participation in either the expert group or DELPHI panel through e-mail. This e-mail will include a summary of the study design, the objectives, and a request for participation. Written consent will be obtained from all individual experts before participation in the procedure. To assure blinding, experts will not be informed about each other's participation. We aim to include at least 15 experts. To ascertain an organized group discussion, we maintain a group maximum of 30 experts.

2.1.3. Delphi-Panel formation

All authors of included articles will be asked to participate in the online survey. Experts will be asked to propose colleagues, researchers and residents. The number of participants in the DELPHI panel is unlimited.
If possible, attendees of relevant congresses (i.e., cost-effectiveness in ortho/neuro/spine-surgery, health economics) will be asked to participate either by a real-time survey.

2.2. Drafting first statements

The research group will draft statements based on information provided by included studies in the systematic literature review. Recommendations will be made concerning, but not limited to, the following topics;

(1) Design and conduct of trial-based economic evaluations
   a. Type of economic evaluation
   b. Method of conduct
   c. Outcome measures
      i. Costs
      ii. Utilities
   d. Treatment characteristics
      i. Surgical
      ii. Post-operative pharmaceuticals
      iii. Additional therapy

(2) Reporting of economic evaluations, as a complement to the CHEERS checklist
   a. Outcomes
   b. Setting

(3) Discussion on methodologic challenges and to define the need for future research.

2.2.1. Validation by expert group

Online survey

Statements drafted by the research group will be sent to the expert group to obtain a level of consensus and feedback. The receival of feedback will take place through a web-based questionnaire. Level of consensus is assessed on a 0 to 10 scale for each statement, in which 0 means "disagree", 5 means "neutral" and 10 means "agree". Experts may provide comments or feedback on statements if desired. Furthermore, all experts will be given the opportunity to suggest additional statements and will be invited to leave further comments or advice for the research group. No discussion is allowed between the experts at this point of time.

Expert meeting

Subsequently, an expert meeting will be held to discuss statements and feedback provided by the expert group. The expert meeting will be led by a member of the research group. Statements will be accepted if the expert group reaches a consensus of more than 75% on the statement[22,25]. If consensus cannot be reached on a proposed statement during the expert meeting, the statements can be discarded, adjusted or reformulated. Steps 2a and 2b can be repeated up to three times[22,25].

2.3. Validation by DELPHI panel

The Delphi method is a structured process, commonly used to develop healthcare quality indicators and consists of four key components: iteration, controlled acquisition of feedback, aggregation of responses, and anonymity. As anonymity might not always be applicable in our situation, we used the term modified[21,25].
All consensus statements are gathered and will be sent to the complete DELPHI panel for final evaluation and validation. Again, all statements reaching consensus of more than 75% will be accepted for the final report. The DELPHI panel will also have the possibility to comment on all statements. This process of evaluation and validation by the DELPHI panel can be repeated multiple times if deemed necessary. If possible, statements will be presented at a congress concerning cost-effectiveness in spine-surgery, to reach a broader audience. Attendees can then vote using a web-based tool to score level of agreement.

2.4. Final report on outcomes

The research group will report on all consensus statements in the form of final recommendations for economic evaluations in spine surgery. This is done preferably in an open-access peer-reviewed renowned scientific journal. A spine-specific checklist can be designed, which includes items to report when performing an economic evaluation. Encountered methodologic challenges and need for further research will be discussed.

2.5. Ethics and dissemination

The final recommendations are intended for (clinical) researchers in the field of cost-effectiveness in spine surgery. However, they can also serve as an example for other disease-specific guidelines. Considering the number of publications addressing the lack in standardized methodology and reporting of cost-effectiveness in spine surgery, the demand for disease-specific guidelines for cost-effectiveness research in spine surgery appears to be high. The Delphi process ensures that researchers in the field are informed of the existence of the project and expected guidelines. Moreover, the Delphi method ensures that the final output reflects the opinions of international participants and gives insight in the adherence level to the recommendations. The aim is to reach uniformity in design, conduct and reporting of these studies, as is currently lacking. This will provide a solid basis to determine cost-effectiveness of spine surgeries and consequently aid to limit the rising healthcare costs. The aim is to publish results in a peer-review journal and to present results at (inter)national conferences.

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APPENDIX FILE 6.1 – SEARCH QUERY

Study population

Spine[Title/Abstract] OR Vertebra*[Title/Abstract] OR cervical spine[Title/Abstract] OR Facet joint[Title/Abstract] OR Cervical vertebrae[Title/Abstract] OR thoracic vertebrae[Title/Abstract] OR lumbar vertebrae[Title/Abstract] OR thoracic spine[Title/Abstract] OR lumbar spine[Title/Abstract] OR sacro*[Title/Abstract] OR spinal sacrum[Title/Abstract] OR sacral[Title/Abstract] OR thoracolumbar[Title/Abstract] OR cervicothoracic[Title/Abstract] OR craniocervical[Title/Abstract] OR intervertebral[Title/Abstract] OR Spondyl* Osteoarthritis, Spine[Title/Abstract] OR radiculopath*[Title/Abstract] OR myelopath*[Title/Abstract] OR herniated disc[Title/Abstract] OR herniated disk[Title/Abstract] OR bulged disc[Title/Abstract] OR slipped disc[Title/Abstract] OR ruptured disc[Title/Abstract] OR nerve root[Title/Abstract] OR kyphos*[Title/Abstract] OR lordosis[Title/Abstract] OR listhes*[Title/Abstract] OR laterolisthes*[Title/Abstract] OR scolios*[Title/Abstract] OR anterolisthes*[Title/Abstract] OR retrolisthes*[Title/Abstract] OR olisthes*[Title/Abstract] OR adjacent segment[Title/Abstract] OR adjacent level[Title/Abstract] OR "Spine" [Mesh] OR "Cervical vertebrae" [Mesh] OR "sacrum" [Mesh] OR "Thoracic Vertebrae" [Mesh] OR "Lumbar Vertebrae" [Mesh] OR "Spondylosis" [Mesh] OR "Osteoarthritis, Spine" [Mesh] OR "Spondylolisthesis" [Mesh] OR "Spinal Cord Compression" [Mesh] OR "Radiculopathy" [Mesh] OR "Intervertebral Disc Displacement" [Mesh] OR "Spinal cord diseases" [Mesh] OR "spinal cord injuries" [Mesh] OR "spinal cord ischemia" [Mesh] OR "Thoracic Vertebrae" [Mesh]

Intervention

Surger*[Title/Abstract] OR Decompress*[Title/Abstract] OR diskectom*[Title/Abstract] OR discectom*[Title/Abstract] OR lamin*[Title/Abstract] OR fusion[Title/Abstract] OR vertebrectom*[Title/Abstract] OR corporectom*[Title/Abstract] OR vertebral condensation*[Title/Abstract] OR interlaminar implant[Title/Abstract] OR interlaminar spacers[Title/Abstract] OR Interlaminar interspinous implant[Title/Abstract] OR stabilization[Title/Abstract] OR stabilization[Title/Abstract] OR cervical arthroplast*[Title/Abstract] OR cervical disc arthroplast*[Title/Abstract] OR "Diskectomy" [Mesh] OR "spinal fusion" [Mesh] OR "surgical procedures, operative" [Mesh] OR "Laminectomy" [Mesh] OR "Total disc replacement" [Mesh] OR "Foraminotomy" [Mesh]

Study Types

Economic[Title/Abstract] OR Charge*[Title/Abstract] OR cost*[Title/Abstract] OR Consumer Price[Title/Abstract] OR Consumption*[Title/Abstract] OR Pricing[Title/Abstract] OR Expenditures[Title/Abstract] OR Macroeconomic[Title/Abstract] OR Microeconomic[Title/Abstract] OR Easterlin Hypothesis[Title/Abstract] OR Decision-analytic model[Title/Abstract] OR Markov[Title/Abstract] OR Budget[Title/Abstract] OR health technolog*[Title/Abstract] OR "Cost-Benefit Analysis" [Mesh] OR "Costs and Cost Analysis" [Mesh] OR "Economics" [Mesh] OR "Health Care Costs" [Mesh] OR "Hospital Costs" [Mesh] OR "Health Expenditures" [Mesh]

Specific guidelines

Guideline [Title/Abstract] OR "Guidelines as Topic"[Mesh]

Specific cost-effectiveness

Economic evaluation [Title/Abstract] OR Decision-analytic model [Title/Abstract] OR Markov[Title/Abstract] OR Cost-Benefit Analysis[Title/Abstract] OR cost-effectiveness analysis[Title/Abstract] OR "Cost-Benefit Analysis" [Mesh] OR "Costs and Cost Analysis" [Mesh] OR "Economics" [Mesh] OR "Health Care Costs" [Mesh] OR "Hospital Costs" [Mesh] OR "Health Expenditures" [Mesh]

Final Search: (A AND B AND C) OR (D AND E)

CHAPTER 7

METHODOLOGY OF ECONOMIC EVALUATIONS IN SPINE SURGERY: A SYSTEMATIC REVIEW AND QUALITATIVE ASSESSMENT

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ABSTRACT

Objectives
The present study is a systematic review conducted as part of a methodological approach to develop evidence-based recommendations for economic evaluations in spine surgery. The aim of this systematic review is to evaluate the methodology and quality of currently available clinical cost-effectiveness studies in spine surgery.

Study design
Systematic literature review.

Data sources
PubMed, Web of Science, Embase, Cochrane, Cumulative Index to Nursing and Allied Health Literature (CINAHL), EconLit, The National Institute for Health Research Economic Evaluation Database (NHS-EED) were searched through 8 December 2022.

Eligibility criteria for selecting studies
Studies were included if they met all of the following eligibility criteria: (i) spine surgery, (ii) the study cost-effectiveness, (iii) clinical study. Model-based studies were excluded.

Data extraction and synthesis
The following data items were extracted and evaluated: pathology, number of participants, intervention(s), year, country, study design, time horizon, comparator(s), utility measurement, effectivity measurement, costs measured, perspective, main result, study quality.

Results
130 economic evaluations were included. Seventy-four of these studies were retrospective studies. The majority of the studies had a time horizon shorter than 2 years. Utility measures varied between the EuroQol 5 dimensions (EQ-5D) and variations of the Short-Form Health Survey (e.g., SF-36). Effect measures varied widely between Visual Analogue Scale (VAS) for pain, Neck Disability Index (NDI), Oswestry Disability Index (ODI), reoperation rates and adverse events. All studies included direct costs from a healthcare perspective. Indirect costs were included in 47 studies. Total Consensus Health Economic Criteria (CHEC) scores ranged from 2 to 18, with a mean score of 12.0 over all 130 studies.

Conclusions
The comparability of economic evaluations in spine surgery is extremely low due to different study designs, follow-up duration and outcome measurements such as utility, effectiveness and costs. This illustrates the need for uniformity in conducting and reporting economic evaluations in spine surgery.

Strengths and limitations of this study

- This is the first study to systematically review the methodology and quality of economic evaluation in the entire field of spine surgery.
- This systematic review was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and executed in accordance with the five-step approach on preparing a systematic review of economic evaluations by Van Mastrigt et al.
- The broad search strategy yielded well over 17,000 unique studies, limiting the probability of missing relevant literature.
- As the scope of this work was limited to assessment of methodology and quality, we did not include results on cost-effectiveness outcomes reported in the studies.
- Risk of bias was not deemed relevant as cost-effectiveness outcomes of the studies were not synthesized in this systematic review. Hence, risk of bias was not included.

1. INTRODUCTION

Economic evaluations are increasingly important considering the growing healthcare expenses. The number of people aged 60 years or older is expected to double by 2050[1]. As older individuals are more likely to require spine surgery, the amount of spine surgeries is also expected to increase. This, in turn, will result in higher healthcare-related costs[2-4]. To limit the increase of spine surgery-related healthcare costs, scarce healthcare resources should be allocated efficiently. Therefore, the most cost-effective surgical technique should be identified and implemented[5,6]. The value of economic evaluations is progressively renowned, as reflected by the observed increase in studies mentioning costs and cost-effectiveness in the last decade[7]. However, previous literature suggests that the variable quality and reporting of these economic evaluations limits their comparability and practicality. Both in cervical and lumbar spine surgery, systematic literature reviews have shown an apparent lack of uniformity[8,9]. This is mainly caused by heterogeneity in study design, study data, hypotheses, and conclusions. An important factor for instance, is the heterogeneity in determining, calculating and reporting cost data[10]. Recent systematic reviews in cervical and lumbar spine surgery show that clinical economic evaluations vary largely in healthcare perspective and societal perspective costs due to differences in calculation methods of costs and/or charges, and differences in in- and exclusion criteria and baseline characteristics[8,9]. The Panel on Cost-Effectiveness in Health and Medicine in the United States recommends performing cost-effectiveness studies from both the healthcare and the societal perspective[11]. Nevertheless, only a minority of economic evaluations report on societal perspective costs[12].

Kepler et al reviewed the existing economic evidence in spine surgery in 2012[13]. This study portrays the lack of homogenous reporting in terms of study design, study population, pathology studied, cost calculations and utility used. Moreover, they observed that only 12% of studies adhered to the recommendations of the US Second Panel of Cost-effectiveness in Health and Medicine. Subsequently, the lack of standardized costing methodology in spine surgery research is also extensively described by Alvin et al and Chang et al.[10,14]. Both suggest several key aspects in cost calculation. First of all, the perspective of included costs should be considered. Secondly, the acquisition and definition of costs should be recognized. Payments, charges, costs and expected reimbursements are separate entities that should not be used synonymously.

General guidelines and recommendations regarding the proper conduct of economic evaluations are available, including the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist, the series of Modelling Good Research Practices published by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) and the recommendations for Conduct, Methodological Practices, and Reporting of Cost-effectiveness Analyses from the Second Panel on Cost-Effectiveness in Health and Medicine[7,11,15]. A limitation of these general guidelines is that by their nature they do not incorporate disease- and topic-specific recommendations[12]. Compared, and in supplement, to the generally accepted methodologic standards, it would thus be

beneficial to have disease-specific guidelines to provide additional recommendations. The lack of homogeneity in economic evaluations regarding spine surgery impedes proper interpretation by healthcare professionals and financial decision-makers. Recommendations to conduct economic evaluations in this field, as a complement to the existing general guidelines, should ameliorate overall research quality, comparability and interpretability.

The present study is a systematic review conducted as part of a methodologic approach to develop evidence-based recommendations for economic evaluations in spine surgery[16]. As a first step, it is of importance to have a complete, up-to-date, overview of current methodology and quality of cost-effectiveness research in spine surgery. As this will enable us to identify the disparity in the current practice and develop adequate recommendations to assess these gaps.

Therefore, the aim of this systematic review is to evaluate the methodology and quality of currently available clinical cost-effectiveness studies in spine surgery. Furthermore, methodological quality of the included clinical studies is assessed according to the Consensus Health Economic Criteria (CHEC)[17]. It should be noted that assessment of the cost-effectiveness of different surgical techniques is not within the scope of this work. We focus solely on the methodology and quality of the studies, as the ultimate goal is to develop a spine-surgery specific guideline for economic evaluations, using a modified Delphi approach. The outcomes of the Delphi approach and the final disease specific guideline will be published separately.

2. MATERIALS AND METHODS

2.1. Review protocol

This systematic review was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and executed in accordance with the five-step approach on preparing a systematic review of economic evaluations by Van Mastrigt et al.[18-22]. The review protocol consisted of a research question, search strategy and eligibility criteria for assessing full-text studies. The complete study protocol has been published beforehand[16].

Since this systematic review is conducted as part of a methodological approach to develop evidence-based recommendations for economic evaluations in spine surgery, a segment of the search is aimed at finding general and disease-specific guidelines on economic evaluations. These studies will be used in drafting statements for a Delphi-analysis, and to identify relevant authors, but will not be included in this systematic review.

2.2. Search strategy and eligibility criteria

The literature search is conducted using several terms, including, but not limited to: "economic evaluation", "cost-effectiveness" and "spine surgery". The full search strategy can be found in Appendix File 7.1. The following databases were searched: PubMed, Web of Science, Embase, Cochrane, Cumulative Index to Nursing and Allied Health Literature (CINAHL), EconLit, The National Institute for Health Research Economic Evaluation Database (NHS-EED).

Our last search was conducted on December 8th, 2022. Studies were included if they met all of the following eligibility criteria: (i) the study concerns spine surgery, (ii) the study investigates and reports on costs and effectiveness, (iii) the study is a clinical study using real world data. In order to provide an up-to-date review of recent studies, we limited the inclusion to studies published in 2011 and onwards. The inclusion of older studies might lead to skewing of data, as methodology and reporting evolve over time.

This review only focusses on trial-based economic evaluations, model-based economic evaluations were thus excluded. This choice was made as the aim of the final guideline is to govern scientists in the conduct and reporting of clinical cost-effectiveness studies.

2.3. Study selection and data collection process

Duplicates were removed. Potentially eligible studies were screened based on title and abstract, this screening was performed by two independent authors amongst 4 authors (VS, RD, AS, IC). If necessary, consensus was reached between both authors through discussion or with assistance of a third reviewer (SH). Final selection of studies based on full-text assessment using the abovementioned eligibility criteria was performed by two authors (VS, RD). Cross-referencing was performed during full-text assessment. Data were collected using a prospectively designed data collection sheet. Data were independently extracted by two authors (VS, RD).

The following data items were considered: pathology, number of included participants, intervention(s) studied, year, country, study design, time horizon, comparator(s), utility measurement, effectivity measurement, costs measured, perspective, main result, and incremental cost-effectiveness ratio (ICER). The complete data collection sheet can be found in Appendix File 7.2.

2.4. Quality assessment

Two authors (VS, RD) independently performed quality assessments on the included studies using The Consensus Health Economic Criteria (CHEC) list[17]. The CHEC-list was chosen as it is the recommended quality-checklist for trial-based economic evaluations[23,24]. A CHEC-score of 19 out of 19 points indicates sublime study quality. The comprehensive description of the CHEC-list and -criteria is displayed in Appendix File 7.3. Full CHEC list scores can be found in Appendix File 7.4. Consensus was reached between both authors through discussion.

2.5. Protocol registration

This review protocol has been published as part of a protocol to develop evidence-based recommendations for economic evaluations in spine surgery[16].

2.6. Patient and public involvement

No patient involved.

3. RESULTS

3.1. Study selection

The systematic database search resulted in 27,036 studies. No additional studies were identified through manual searches of relevant reference lists. Results of the study selection process are summarized in Figure 7.1. After removing duplicates 17,746 studies were screened on title and abstract. In total, 510 studies were eligible for full-text analysis, resulting in exclusion of 380 studies; 139 studies were studies other than clinical trials, 72 studies did not report on an effectivity outcome measure, 50 studies used similar datasets as prior included studies or were duplicates, 47 studies were model-based, 21 studies were abstract-only, 11 studies did not concern spine surgery, and 5 studies did not mention costs. Thirty-five studies were identified as useful guidelines on economic evaluations, but were not included in this systematic review. They will be used in a separate study to develop evidence-based recommendations for economic evaluations in spine surgery. Finally, a total of 130 clinical cost-effectiveness studies were included[25-154].

3.2. Study characteristics – clinical studies

Table 7.1 displays the study characteristics of the included clinical cost-effectiveness studies. The majority of the studies (n=74) were conducted in the United States of America (USA) and Europe (n=28). Of the 130 studies, 74 were retrospective analyses, 22 were trial-based models, 22 were prospective cohorts, 12 were randomized controlled trials (RCTs). Most studies concerned lumbosacral spine surgery (n=68), fewer studies concerned cervical (n=23) and spinal deformity surgery (n=22). The majority of the studies had a time horizon of two years or shorter (n=95). The EuroQol 5 dimensions (EQ-5D) was the most frequently used utility measurement (n=46) in combination with the variations of the Short-Form Health Survey (e.g., SF-36, SF-6D) (n=43). Effect measures varied widely between Visual Analogue Scale (VAS) for pain, Neck Disability Index (NDI), Oswestry Disability Index (ODI), reoperation rates and adverse events. All studies included direct costs from a healthcare perspective.
Costs of hospitalization (n=81), procedure (n=70) and pharmaceuticals (n=50) were most often included as direct costs, followed by costs of diagnostics (n=46) and outpatient

visits (n=48). In 26 studies, it was not specified which costs were evaluated. A limited number of studies included costs associated with revision surgery, reoperations, readmissions, complications and use of medical devices. Indirect costs were included in 47 studies, of which 41 studies adapted a societal perspective. The indirect costs evaluated mainly consisted of loss of productivity (n=44).

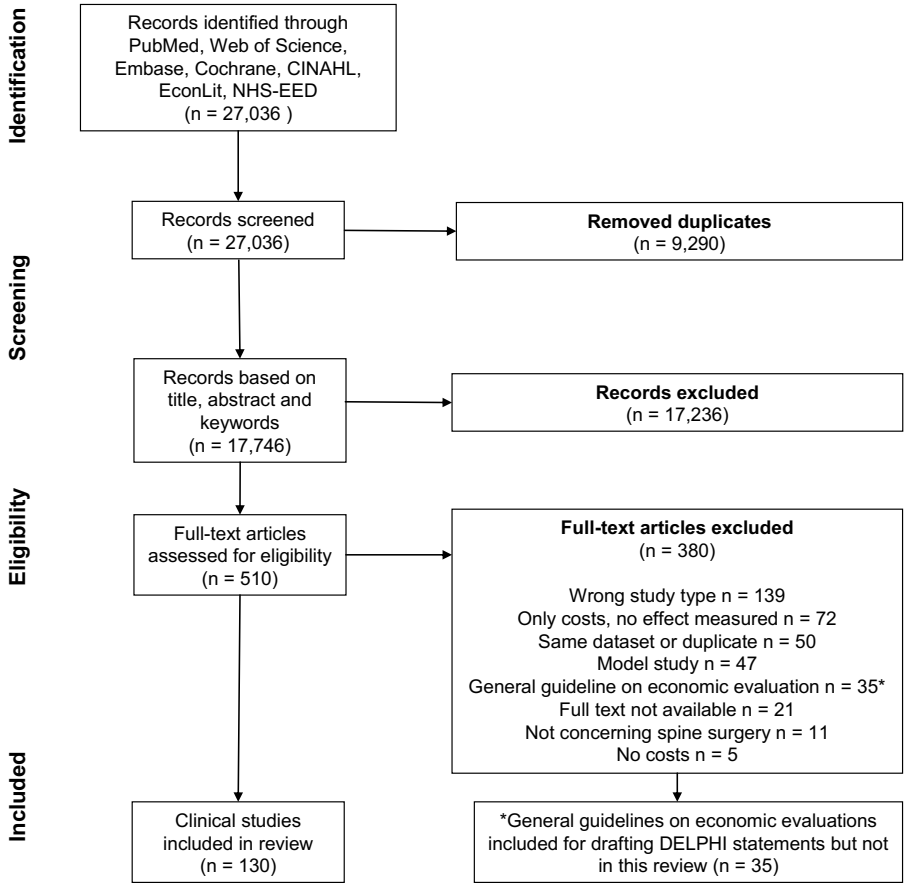

Figure 7.1 - PRISMA Flowchart

The majority of cost data were collected from the hospital records (n=63) and Medicare records (n=49). Other used cost data sources were; Diagnose Related Group codes (DRG, n=35), Current Procedural Terminology (CPT, n=25) and national or regional databases (n=22). Indirect cost data of lost productivity was estimated based on average wages in most studies. Several studies used patient reported wages. The complete data extraction sheet of the included studies is summarized in Appendix File 7.2.

Table 7.1 - Characteristics of the included studies.

Study Characteristics	Nr. of studies (n=)	Subgroups	Nr. of studies (n=)
Continent		**Country**	
North America	81	USA	74
		Canada	7
South America	1	Brazil	1
Europe	28	Belgium	1
		Denmark	4
		France	1
		Germany	3
		Italy	1
		Norway	2
		Portugal	1
		Spain	2
		Sweden	2
		Switzerland	2
		The Netherlands	4
		United Kingdom	5
Asia	19	China	4
		Japan	8
		Korea	6
		Turkey	1
Africa	1	Tanzania	1
Year			
2010-2015	37		
2015-2020	59		
>2020	34		
Topic			
Cervical	23		
Lumbosacral	68		
Spinal deformity / Scoliosis	22		
(Osteoporotic) Fractures	10		
Oncology	4		
Other	3		
Study Design			
Retrospective analysis	74		
Prospective cohort	22		
Randomized Controlled Trial	12		
Trial based model	22		
Time horizon			
< 1 year	41		
1-2 years	54		
2-5 years	17		
5-10 years	14		
> 10 years	4		
Utility measurement			
EuroQol 5 Dimensions (EQ-5D)	46		
Short Form (SF)	43		
Oswestry Disablility Index (ODI)	12		
Roland Morris Score (RDS)	1		
Scoliosis Research Society Patient Questionnaire	1		
Effect measurement Tool			
Visual Analogue Scale (VAS)	31		
Short Form (SF)	3		
Oswestry Disablility Index (ODI)	21		
Adverse Events (AE)	19		
Neck Disability Index (NDI)	7		
Reoperations	11		
Frankel	3		
Karnofsky Performance Score (KPS)	1		

Table 7.1 - (continued)

Study Characteristics	Nr. of studies (n=)	Subgroups	Nr. of studies (n=)
Perspective			
Healthcare	130		
Societal	41		
Costs included			
Direct	130	Hospitalization	81
		Procedure	70
		Pharmaceuticals	50
		Diagnostics	46
		Outpatient visits	48
		Physician fee	33
		Paramedic therapy	27
		Implants and materials	29
		Emergency Room visits	22
		Spinal injections	23
		Revision and/or reoperations	15
		Readmissions	17
		Complications	13
		Medical devices	8
		Not specified	26
Indirect	47	Loss of productivity	44
		Unpaid caregivers	16
		Transport	5
		Out of pocket expenses	4
		Paid caregivers	3
		Rehabilitation	2
		Not specified	2
Cost data source			
Hospital records / financial department	63		
Medicare	49		
Diagnosis related group (DRG)	35		
Current Procedural Terminology (CPT)	25		
Average wages	19		
National databases	16		
Redbook	12		
Patient reported resource utilization	10		
Regional databases	6		
Actual wages	6		
International Statistical Classification of Diseases (ICD) codes	4		
Private insurance data	3		
Military records	1		
Other publications	2		
Not specified	14		

3.3. Quality of identified studies

The methodological quality of the included clinical studies was assessed according to the CHEC-Criteria[17]. Study protocols for clinical economic evaluation studies were similarly assessed. The complete CHEC scores of included studies are summarized in Appendix File 7.4. Total CHEC scores ranged from 2 to 18, with a mean score of 12.0 over all 130 studies. The scores for randomized controlled trials ranged from 5 to 18, with a mean of 13.7. The scores for prospective cohort studies ranged from seven to 15, with a mean of

12.2. The scores for retrospective studies ranged from two to 17, with a mean of 10.9. A comprehensive overview of total score per study is depicted in Figure 7.2.

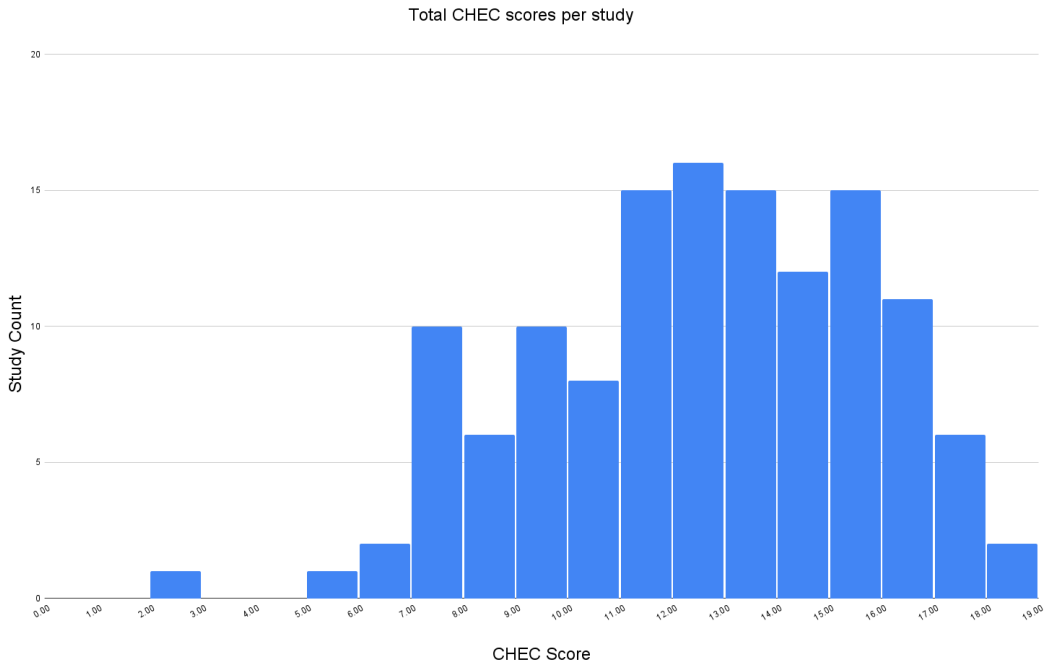

Figure 7.2 - Total score per study.

Several domains of the CHEC criteria were scored in less than half of the included studies; study design (n=50), perspective (n=42), reporting of ICER (n=65), discounting (n=58), sensitivity analysis (n=57), and ethical considerations (n=4). Various domains were scored in over 80% of the studies; study population (n=124), research question (n=124), study outcome (n=115), measurement of outcome (n=113), value of outcome (n=107), conclusion (n=114). A comprehensive overview of total score per domain is depicted in Figure 7.3.

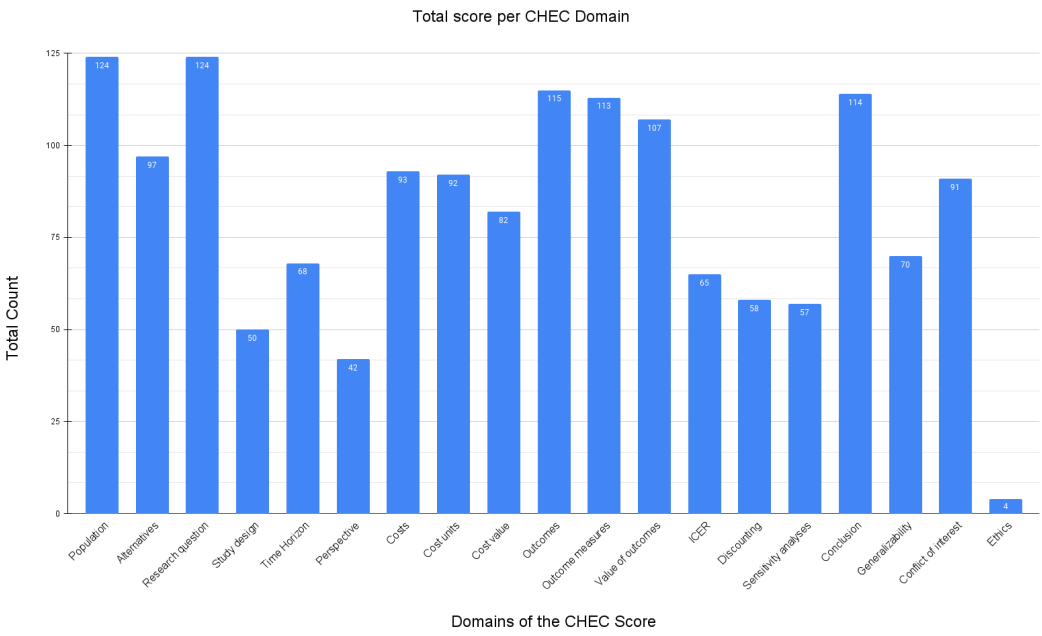

Figure 7.3 – Total score per domain.

4. DISCUSSION

This study provides an extensive and up to date overview of the methodology and quality of cost-effectiveness research in spine surgery. Although this is not the first review that describes the current literature concerning cost-effectiveness in spine surgery, it adds new information to the existing literature, as it focusses on the methodology and quality of all clinical economic evaluations in spine surgery. The search conducted for this review was very broad, which resulted in a high number of hits over the different databases. Logically, this has led to a much higher inclusion rate than previous reviews on the topic[10,13]. As can be deducted from Table 7.1, the number of publications concerning cost-effectiveness in spine surgery appears to be increasing over recent years. This was similarly described by Husereau et al.[7]. No additional studies were found through cross-referencing, as all studies found through cross-referencing were already found in the initial search.

We encountered 12 systematic reviews on the subject while screening articles found in our search. Of these studies 6 reviewed cost-effectiveness of minimally invasive spine surgery[6-9,154-157], two reviewed lumbar spine surgery for spondylolisthesis[158,159], two reviewed all cost-effectiveness studies in spine surgery in the USA[14,160], one reviewed cervical degenerative disease[161], and one reviewed vertebroplasty and balloon kyphoplasty for osteoporotic vertebral compression fractures[162].

The number of included studies in each review ranged from 5 to 58 studies, with a mean of 22 included studies per review. One study did not mention the total number of studies included[155].

For quality assessment, four reviews used the Quality of Health Economic Studies (QHES)[10,154,158,160-163], two reviews used the Consensus Health Economic Criteria (CHEC[17])[9,161], one review used the Consolidated Health Economic Evaluation Reporting Standards (CHEERS[7])[14], one review used the Grading of Recommendations Assessment, development and Evaluation (GRADE)[156,164], and one review used a Cochrane Working Group Tool[157,165]. The remaining three studies did not assess study quality[6,155,162]. All preceding systematic reviews on the cost-effectiveness in spine surgery conclude that the quality of the economic evaluations in the field is low to moderate. As a consequence, none of the reviews are able to draw firm conclusions based on the existing literature. Furthermore, the majority of these reviews conclude that economic evaluation studies of higher quality are required.

Amongst the included economic evaluations in this systematic review, there is a high degree of variation in study designs. The majority of studies are retrospective analyses, which is regarded suboptimal for the evaluation of cost-effectiveness. Thereby, there is also a large variation in the time-horizon used amongst the studied economic evaluations. It is noteworthy that the majority of studies has a follow-up period of less than two years. In spine surgery, and in cost-effectiveness research specifically, it is recommended to incorporate an adequate follow-up duration, which is recommended to be at least two to four years[166]. Moreover, an adequate choice of both the intervention and comparator is essential for the conduct of a proper cost-utility analysis (CUA) or cost-effectiveness analysis (CEA)[167]. The use of utility and effectivity measurement tools is highly inconsistent. One of the included studies even showed that the ICER differed strongly depending on the use of NDI or SF-36, when they were both evaluated[168]. Another study also showed a significant difference in cost-effectiveness depending on the use of utility measurement: when using EQ-5D, the intervention was cost-effective, however it was not cost-effective when using SF-6D[96]. This shows that utility measurements cannot be used interchangeably, and consequently the ICERs cannot be compared between studies. Moreover, there is no equality in the costs, charges and/or reimbursements included in the studies. Not even half of the included studies included a societal perspective, despite this being strongly recommended[11]. As seen in Table 7.1, consistency in the use and reporting of direct and indirect costs is lacking. Moreover, cost data is collected from various sources in multiple ways. Noteworthy, many studies did not specify the included costs data and data sources. Some of the studies also considered the inclusion of "indirect" hospital costs (e.g. washing of bed linen) as the inclusion of indirect costs, thus wrongfully reported the study to be conducted from a societal perspective[169].

The difference of included cost utility and/or effectivity measurements, causes the denominator and the divisor to vary so strongly that no conclusions can be drawn concerning cost-effectiveness. Considering that back-related complaints are the leading

cause for disability globally, it is astonishing to see that there is no consensus concerning cost-effectiveness in spine surgery[170]. Even the high(er) quality economic evaluations do not provide sufficient insight at this moment, as the outcomes are not comparable to any other studies. Taking into account all of the study characteristics and outcome measurements, barely any outcomes of the 108 included studies concerning cost-effectiveness in spine surgery can be compared. This reveals the current absence in government, or anarchy, in the conduct of cost-effectiveness research.

The quality of the studies based on the CHEC criteria is low to moderate. Only a limited number of studies is of high quality. It is noticeable that several domains of the CHEC criteria were scored in less than half of the included studies. Especially domains that are highly specific for cost-effectiveness studies were lacking. For example, the use of discounting and performing a sensitivity analysis were specifically deficient in many studies[171-173]. Apparently, judging the heterogeneity and quality in the current literature, general guidelines are insufficiently adhered to or too unspecific. We advocate that not only studies of higher quality, but especially of higher comparability are required to determine the cost-effectiveness of interventions in spine surgery.

As mentioned in the introduction of this paper, the lack of homogeneity in economic evaluations regarding spine surgery impedes proper interpretation by healthcare professionals and financial decision-makers. This lack of homogeneity has been mentioned numerous times in previous systematic reviews, and is once again confirmed by this present review. To ameliorate the research quality, comparability and interpretability, disease-specific recommendations for the conduct of economic evaluations in the field of spine surgery, as complement to existing general guidelines, are needed. These recommendations will be developed by a group of experts and validated in a Delphi process. By gathering a diverse group of experts that will reach consensus concerning methodology in cost-effectiveness research, variability of future studies can be reduced, thus increasing overall research quality.

The outcomes of this review serve as a basis to develop these evidence-based recommendations for economic evaluations in spine surgery[16].

4.1. Limitations

This systematic review is subject to several constraints. We did not perform an in-depth review of the content of the included studies since the purpose of this study was to evaluate the methodological quality of the economic evaluations specifically. Besides, the great variety in interventions and comparators among the included studies impedes proper topic-specific in-depth reviews of the content of these studies. Assessing the risk of bias is of limited value in this review, as this concerns robustness of the outcomes and conclusions of a study. Whereas we solely focused on the methodology and quality of the studies, we did not perform a risk of bias assessment. We suggest that topic-specific systematic reviews on cost-effectiveness of the various interventions in spine surgery are to be performed separately.

This systematic review on cost-effectiveness studies in spine surgery was limited to clinical studies and previously published systematic reviews and does therefore not include model-based studies. Several model-based studies are based on clinical trial data, these trial-based model studies were thus included. The exclusion of model-based studies logically limits the conclusions of this work to clinical economic evaluation studies. We choose to exclude model studies as the aim of our guideline is to govern scientists in the conduct and reporting of clinical cost-effectiveness studies. We believe that the current limitations in cost-effectiveness research arise form study design and data collection in clinical studies, rather than modelling. Additionally, we are of the opinion that general guidelines for modelling are sufficient.

5. CONCLUSION

This systematic review shows that the number of economic evaluations in the field of spine surgery is increasing. However, the quality of these studies remains low to moderate. More importantly, the comparability of the study remains extremely low due to different study designs, follow-up duration and outcome measurements such as utility, effectiveness and costs. As a result of these differences in methodology and reporting, current studies are not comparable. This illustrates the current anarchy in cost-effectiveness research and the consequent need for uniformity in conduct and reporting of economic evaluations in spine surgery.

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APPENDIX FILE 7.1 – REVIEW SEARCH

Study population

Spine[Title/Abstract] OR Vertebra*[Title/Abstract] OR cervical spine[Title/Abstract] OR Facet joint[Title/Abstract] OR Cervical vertebrae[Title/Abstract] OR thoracic vertebrae[Title/Abstract] OR lumbar vertebrae[Title/Abstract] OR thoracic spine[Title/Abstract] OR lumbar spine[Title/Abstract] OR sacro*[Title/Abstract] OR spinal sacrum[Title/Abstract] OR sacral[Title/Abstract] OR thoracolumbar[Title/Abstract] OR cervicothoracic[Title/Abstract] OR craniocervical[Title/Abstract] OR intervertebral[Title/Abstract] OR Spondyl* Osteoarthritis, Spine[Title/Abstract] OR radiculopath*[Title/Abstract] OR myelopath*[Title/Abstract] OR herniated disc[Title/Abstract] OR herniated disk[Title/Abstract] OR bulged disc[Title/Abstract] OR slipped disc[Title/Abstract] OR ruptured disc[Title/Abstract] OR nerve root[Title/Abstract] OR kyphos*[Title/Abstract] OR lordosis[Title/Abstract] OR listhes*[Title/Abstract] OR laterolisthes*[Title/Abstract] OR scolios*[Title/Abstract] OR anterolisthes*[Title/Abstract] OR retrolisthes*[Title/Abstract] OR olisthes*[Title/Abstract] OR adjacent segment[Title/Abstract] OR adjacent level[Title/Abstract] OR "Spine" [Mesh] OR "Cervical vertebrae" [Mesh] OR "sacrum" [Mesh] OR "Thoracic Vertebrae" [Mesh] OR "Lumbar Vertebrae" [Mesh] OR "Spondylosis" [Mesh] OR "Osteoarthritis, Spine" [Mesh] OR "Spondylolisthesis" [Mesh] OR "Spinal Cord Compression" [Mesh] OR "Radiculopathy" [Mesh] OR "Intervertebral Disc Displacement" [Mesh] OR "Spinal cord diseases" [Mesh] OR "spinal cord injuries" [Mesh] OR "spinal cord ischemia" [Mesh] OR "Thoracic Vertebrae" [Mesh]

Intervention

Surger*[Title/Abstract] OR Decompress*[Title/Abstract] OR diskectom*[Title/Abstract] OR discectom*[Title/Abstract] OR lamin*[Title/Abstract] OR fusion[Title/Abstract] OR vertebrectom*[Title/Abstract] OR corporectom*[Title/Abstract] OR vertebral condensation*[Title/Abstract] OR interlaminar implant[Title/Abstract] OR interlaminar spacers[Title/Abstract] OR Interlaminar interspinous implant[Title/Abstract] OR stabilization[Title/Abstract] OR stabilization[Title/Abstract] OR cervical arthroplast*[Title/Abstract] OR cervical disc arthroplast*[Title/Abstract] OR "Diskectomy" [Mesh] OR "spinal fusion" [Mesh] OR "surgical procedures, operative" [Mesh] OR "Laminectomy" [Mesh] OR "Total disc replacement" [Mesh] OR "Foraminotomy" [Mesh]

Study Types

Economic[Title/Abstract] OR Charge*[Title/Abstract] OR cost*[Title/Abstract] OR Consumer Price[Title/Abstract] OR Consumption*[Title/Abstract] OR Pricing[Title/Abstract] OR Expenditures[Title/Abstract] OR Macroeconomic[Title/Abstract] OR Microeconomic[Title/Abstract] OR Easterlin Hypothesis[Title/Abstract] OR Decision-analytic model[Title/Abstract] OR Markov[Title/Abstract] OR Budget[Title/Abstract] OR health technolog*[Title/Abstract] OR "Cost-Benefit Analysis" [Mesh] OR "Costs and Cost Analysis" [Mesh] OR "Economics" [Mesh] OR "Health Care Costs" [Mesh] OR "Hospital Costs" [Mesh] OR "Health Expenditures" [Mesh]

Specific guidelines

(Guideline [Title/Abstract] OR "Guidelines as Topic"[Mesh])

Specific cost-effectiveness
(Economic evaluation [Title/Abstract] OR Decision-analytic model [Title/Abstract] OR Markov[Title/Abstract] OR Cost-Benefit Analysis[Title/Abstract] OR cost-effectiveness analysis[Title/Abstract] OR "Cost-Benefit Analysis" [Mesh] OR "Costs and Cost Analysis" [Mesh] OR "Economics" [Mesh] OR "Health Care Costs" [Mesh] OR "Hospital Costs" [Mesh] OR "Health Expenditures" [Mesh])

D+E
(Guideline [Title/Abstract] OR "Guidelines as Topic"[Mesh]) AND (Economic evaluation [Title/Abstract] OR Decision-analytic model[Title/Abstract] OR Markov[Title/Abstract] OR Cost-Benefit Analysis[Title/Abstract] OR cost-effectiveness analysis[Title/Abstract] OR "Cost-Benefit Analysis" [Mesh] OR "Costs and Cost Analysis" [Mesh] OR "Economics" [Mesh] OR "Health Care Costs" [Mesh] OR "Hospital Costs" [Mesh] OR "Health Expenditures" [Mesh])

PubMed Search: 9,701 hits

Total (Last 10 years)

(((Spine[Title/Abstract] OR Vertebra*[Title/Abstract] OR cervical spine[Title/Abstract] OR Facet joint[Title/Abstract] OR Cervical vertebrae[Title/Abstract] OR thoracic vertebrae[Title/Abstract] OR lumbar vertebrae[Title/Abstract] OR thoracic spine[Title/Abstract] OR lumbar spine[Title/Abstract] OR sacro*[Title/Abstract] OR spinal sacrum[Title/Abstract] OR sacral[Title/Abstract] OR thoracolumbar[Title/Abstract] OR cervicothoracic[Title/Abstract] OR craniocervical[Title/Abstract] OR intervertebral[Title/Abstract] OR Spondyl* Osteoarthritis, Spine[Title/Abstract] OR radiculopath*[Title/Abstract] OR

myelopath*[Title/Abstract] OR herniated disc[Title/Abstract] OR herniated disk[Title/Abstract] OR bulged disc[Title/Abstract] OR slipped disc[Title/Abstract] OR ruptured disc[Title/Abstract] OR nerve root[Title/Abstract] OR kyphos*[Title/Abstract] OR lordosis[Title/Abstract] OR listhes*[Title/Abstract] OR laterolisthes*[Title/Abstract] OR scolios*[Title/Abstract] OR anterolisthes*[Title/Abstract] OR retrolisthes*[Title/Abstract] OR olisthes*[Title/Abstract] OR adjacent segment[Title/Abstract] OR adjacent level[Title/Abstract] OR "Spine" [Mesh] OR "Cervical vertebrae" [Mesh] OR "sacrum" [Mesh] OR "Thoracic Vertebrae" [Mesh] OR "Lumbar Vertebrae" [Mesh] OR "Spondylosis" [Mesh] OR "Osteoarthritis, Spine" [Mesh] OR "Spondylolisthesis" [Mesh] OR "Spinal Cord Compression" [Mesh] OR "Radiculopathy" [Mesh] OR "Intervertebral Disc Displacement" [Mesh] OR "Spinal cord diseases" [Mesh] OR "spinal cord injuries" [Mesh] OR "spinal cord ischemia" [Mesh] OR "Thoracic Vertebrae" [Mesh]) AND (Surger*[Title/Abstract] OR Decompress*[Title/Abstract] OR diskectom*[Title/Abstract] OR discectom*[Title/Abstract] OR lamin*[Title/Abstract] OR fusion[Title/Abstract] OR vertebrectom*[Title/Abstract] OR corporectom*[Title/Abstract] OR vertebral condensation*[Title/Abstract] OR interlaminar implant[Title/Abstract] OR interlaminar spacers[Title/Abstract] OR Interlaminar interspinous implant[Title/Abstract] OR stabilization[Title/Abstract] OR stabilization[Title/Abstract] OR cervical arthroplast*[Title/Abstract] OR cervical disc arthroplast*[Title/Abstract] OR "Diskectomy" [Mesh] OR "spinal fusion" [Mesh] OR "surgical procedures, operative" [Mesh] OR "Laminectomy" [Mesh] OR "Total disc replacement" [Mesh] OR "Foraminotomy" [Mesh])) AND (Economic[Title/Abstract] OR Charge*[Title/Abstract] OR cost*[Title/Abstract] OR Consumer Price[Title/Abstract] OR Consumption*[Title/Abstract] OR Pricing[Title/Abstract] OR Expenditures[Title/Abstract] OR Macroeconomic[Title/Abstract] OR Microeconomic[Title/Abstract] OR Easterlin Hypothesis[Title/Abstract] OR Decision-analytic model[Title/Abstract] OR Markov[Title/Abstract] OR Budget[Title/Abstract] OR health technolog*[Title/Abstract] OR "Cost-Benefit Analysis" [Mesh] OR "Costs and Cost Analysis" [Mesh] OR "Economics" [Mesh] OR "Health Care Costs" [Mesh] OR "Hospital Costs" [Mesh] OR "Health Expenditures" [Mesh])) OR ((Guideline [Title/Abstract] OR "Guidelines as Topic"[Mesh]) AND (Economic evaluation [Title/Abstract] OR Decision-analytic model[Title/Abstract] OR Markov[Title/Abstract]OR Cost-Benefit Analysis[Title/Abstract] OR cost-effectiveness analysis[Title/Abstract] OR "Cost-Benefit Analysis" [Mesh] OR "Costs and Cost Analysis" [Mesh] OR "Economics" [Mesh] OR "Health Care Costs" [Mesh] OR "Hospital Costs" [Mesh] OR "Health Expenditures" [Mesh]))

Web of Science (2011-2021)

Topic (Title, abstract, highlights):

((Spine OR Vertebra* OR cervical spine OR Facet joint OR Cervical vertebrae OR thoracic vertebrae OR lumbar vertebrae OR thoracic spine OR lumbar spine OR sacro* OR spinal sacrum OR sacral OR thoracolumbar OR cervicothoracic OR craniocervical OR intervertebral OR Spondyl* Osteoarthritis, Spine OR radiculopath* OR myelopath* OR herniated disc OR herniated disk OR bulged disc OR slipped disc OR ruptured disc OR nerve root OR kyphos* OR lordosis OR listhes* OR laterolisthes* OR scolios* OR anterolisthes* OR retrolisthes* OR olisthes* OR adjacent segment OR adjacent level) AND (Surger* OR Decompress* OR diskectom* OR discectom* OR lamin* OR fusion OR vertebrectom* OR corporectom* OR vertebral condensation* OR interlaminar implant OR interlaminar spacers OR Interlaminar interspinous implant OR stabilization OR stabilization OR cervical arthroplast* OR cervical disc arthroplast*) AND (Economic OR Charge* OR cost* OR Consumer Price OR Consumption* OR Pricing OR Expenditures OR Macroeconomic OR Microeconomic OR Easterlin Hypothesis OR Decision-analytic model OR Markov OR Budget OR health technolog*)) OR ((Economic evaluation OR Decision-analytic model OR Markov OR Cost-Benefit Analysis OR cost-effectiveness analysis) AND (guideline))

Hits: 9,684

Embase (2011-2021)

Abstract:
((Spine OR Vertebra* OR cervical spine OR Facet joint OR Cervical vertebrae OR thoracic vertebrae OR lumbar vertebrae OR thoracic spine OR lumbar spine OR sacro* OR spinal sacrum OR sacral OR thoracolumbar OR cervicothoracic OR craniocervical OR intervertebral OR Spondyl* Osteoarthritis, Spine OR radiculopath* OR myelopath* OR herniated disc OR herniated disk OR bulged disc OR slipped disc OR ruptured disc OR nerve root OR kyphos* OR lordosis OR listhes* OR laterolisthes* OR scolios* OR anterolisthes* OR retrolisthes* OR olisthes* OR adjacent segment OR adjacent level) AND (Surger* OR Decompress* OR diskectom* OR discectom* OR lamin* OR fusion OR vertebrectom* OR corporectom* OR vertebral condensation* OR interlaminar implant OR interlaminar spacers OR Interlaminar interspinous implant OR stabilization OR stabilization OR cervical arthroplast* OR cervical disc arthroplast*) AND (Economic OR Charge* OR cost* OR Consumer Price OR Consumption* OR Pricing OR Expenditures OR Macroeconomic OR Microeconomic OR Easterlin Hypothesis OR Decision-analytic model OR Markov OR Budget OR health technolog*)) OR ((Economic evaluation OR Decision-analytic model OR Markov OR Cost-Benefit Analysis OR cost-effectiveness analysis) AND (guideline))

Hits: 101 Hits

Cochrane (2011-2021)

Title and abstract:
((Spine OR Vertebra* OR cervical spine OR Facet joint OR Cervical vertebrae OR thoracic vertebrae OR lumbar vertebrae OR thoracic spine OR lumbar spine OR sacro* OR spinal sacrum OR sacral OR thoracolumbar OR cervicothoracic OR craniocervical OR intervertebral OR Spondyl* Osteoarthritis, Spine OR radiculopath* OR myelopath* OR herniated disc OR herniated disk OR bulged disc OR slipped disc OR ruptured disc OR nerve root OR kyphos* OR lordosis OR listhes* OR laterolisthes* OR scolios* OR anterolisthes* OR retrolisthes* OR olisthes* OR adjacent segment OR adjacent level) AND (Surger* OR Decompress* OR diskectom* OR discectom* OR lamin* OR fusion OR vertebrectom* OR corporectom* OR vertebral condensation* OR interlaminar implant OR interlaminar spacers OR Interlaminar interspinous implant OR stabilization OR stabilization OR cervical arthroplast* OR cervical disc arthroplast*) AND (Economic OR Charge* OR cost* OR Consumer Price OR Consumption* OR Pricing OR Expenditures OR Macroeconomic OR Microeconomic OR Easterlin Hypothesis OR Decision-analytic model OR Markov OR Budget OR health technolog*)) in Title Abstract Keyword OR ((Economic evaluation OR Decision-analytic model OR Markov OR Cost-Benefit Analysis OR cost-effectiveness analysis) AND (guideline)) in Title Abstract Keyword - (Word variations have been searched)

Hits: 31 cochrane reviews, 1275 trials

CINAHL (2011-2021)

AB ((Spine OR Vertebra* OR cervical spine OR Facet joint OR Cervical vertebrae OR thoracic vertebrae OR lumbar vertebrae OR thoracic spine OR lumbar spine OR sacro* OR spinal sacrum OR sacral OR thoracolumbar OR cervicothoracic OR craniocervical OR intervertebral OR Spondyl* Osteoarthritis, Spine OR radiculopath* OR myelopath* OR herniated disc OR herniated disk OR bulged disc OR slipped disc OR ruptured disc OR nerve root OR kyphos* OR lordosis OR listhes* OR laterolisthes* OR scolios* OR anterolisthes* OR retrolisthes* OR olisthes* OR adjacent segment OR adjacent level) AND AB (Surger* OR Decompress* OR diskectom* OR discectom* OR lamin* OR fusion OR vertebrectom* OR corporectom* OR vertebral condensation* OR interlaminar implant OR interlaminar spacers OR Interlaminar interspinous implant OR stabilization OR stabilization OR cervical arthroplast* OR cervical disc arthroplast*) AND AB (Economic OR Charge* OR cost* OR Consumer Price OR Consumption* OR Pricing OR Expenditures OR Macroeconomic OR Microeconomic OR Easterlin Hypothesis OR Decision-analytic model OR Markov OR Budget OR health technolog*)) OR AB ((Economic evaluation OR Decision-analytic model OR Markov OR Cost-Benefit Analysis OR cost-effectiveness analysis) AND AB Guideline)

Hits: 1669

EconLit (2011-2021)

Spine OR vertebra* OR facet joint OR sacro* OR spinal OR sacral OR spondyl* OR sclios* OR radiculopathy OR disc
Surger* OR decompress* OR discec* OR lamin* OR fusion OR laminect*
Guideline OR recommendation (all tiab)
Economic evaluation OR Decision-analytic model OR Markov OR Cost-Benefit Analysis OR cost-effectiveness analysis (all tiab)

Hits: 209

NHS-EED (2011-2021)

Any field:
((Spine OR Vertebra* OR cervical spine OR Facet joint OR Cervical vertebrae OR thoracic vertebrae OR lumbar vertebrae OR thoracic spine OR lumbar spine OR sacro* OR spinal sacrum OR sacral OR thoracolumbar OR cervicothoracic OR craniocervical OR intervertebral OR Spondyl* Osteoarthritis, Spine OR radiculopath* OR myelopath* OR herniated disc OR herniated disk OR bulged disc OR slipped disc OR ruptured disc OR nerve root OR kyphos* OR lordosis OR listhes* OR laterolisthes* OR scolios* OR anterolisthes* OR retrolisthes* OR olisthes* OR adjacent segment OR adjacent level) AND (Surger* OR Decompress* OR diskectom* OR discectom* OR lamin* OR fusion OR vertebrectom* OR corporectom* OR vertebral condensation* OR interlaminar implant OR interlaminar spacers OR Interlaminar interspinous implant OR stabilization OR stabilization OR cervical arthroplast* OR cervical disc arthroplast*) AND (Economic OR Charge* OR cost* OR Consumer Price OR Consumption* OR Pricing OR Expenditures OR Macroeconomic OR Microeconomic OR Easterlin Hypothesis OR Decision-analytic model OR Markov OR Budget OR health technolog*)) OR ((Economic evaluation OR Decision-analytic model OR Markov OR Cost-Benefit Analysis OR cost-effectiveness analysis) AND (guideline))

Hits: 182

APPENDIX FILE 7.2 - DATA EXTRACTION SHEET

See the link below:
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10040072/

APPENDIX FILE 7.3 - CHEC LIST

	CHEC-list	YES	NO
1.	Is the study population clearly described?		
2.	Are competing alternatives clearly described?		
3.	Is a well-defined research question posed in answerable form?		
4.	Is the economic study design appropriate to the stated objective?		
5.	Is the chosen time horizon appropriate in order to include relevant costs and consequences?		
6.	Is the actual perspective chosen appropriate?		
7.	Are all important and relevant costs for each alternative identified?		
8.	Are all costs measured appropriately in physical units?		
9.	Are costs valued appropriately?		
10.	Are all important and relevant outcomes for each alternative identified?		
11.	Are all outcomes measured appropriately?		
12.	Are outcomes valued appropriately?		
13.	Is an incremental analysis of costs and outcomes of alternatives performed?		
14.	Are all future costs and outcomes discounted appropriately?		
15.	Are all important variables, whose values are uncertain, appropriately subjected to sensitivity analysis?		
16.	Do the conclusions follow from the data reported?		
17.	Does the study discuss the E of the results to other settings and patient/client groups?		
18.	Does the article indicate that there is no potential conflict of interest of study researcher(s) and funder(s)?		
19.	Are ethical and distributional issues discussed appropriately?		

Assessment instruction

The CHEC-list consists of 19 yes-or-no questions one for each category. In some cases insufficient information is available in the article, or in other published material. In those cases the assessor has to tick 'no'. The assessor should state 'yes' if they agree that the study paid sufficient attention to a certain aspect. To help the assessor when filling out the CHEC-list an explanation of the meaning of each item is given in below.

1. The relevant clinical characteristics, entry and eligibility criteria, as well as drop-out during follow-up should be stated explicitly.
2. A detailed description should be given of the competing interventions. This should encompass a clear and specific statement of the primary objective of each alternative, as well as relevant factors, such as intensity, duration, and frequency.
3. A research question has to identify clearly the alternatives being compared and the population for which the comparison is made.
4. An appropriate economic study design is a full economic evaluation (comparison of costs and effects of 2 or more interventions) based on primary research (cohort, case-control, randomised controlled trial).
5. The period of analysis of the study is the time horizon. This time horizon should always be equal for costs and outcomes if these are combined in a ratio. The time span should be long enough to include all relevant costs and outcomes relating the intervention. Ideally, the follow-up period should be extended till the situation is stabilised with reference to costs and effects.
6. 'Perspective' indicates from which point of view an economic evaluation study is performed. If the study is performed from a societal perspective tick 'yes', as all relevant costs and consequences of an interventions and disease are taken into account, if possible. Other narrower perspectives will only include certain components. The authors should motivate why a narrower perspective is valid.
7. A full identification of all important and relevant costs should be given in relation to the perspective and the research question.
8. The costs should be measured appropriately in physical units. The instrument by which the costs are measured should be valid and clearly stated (e.g. interview, questionnaire, cost-diary).
9. The sources of valuation should be clearly stated for each cost price of every volume parameter and their reference year. The main cost should be calculated based on depleted sources, no tariffs should be used.
10. A full identification of all important and relevant outcomes should be given in relation to the perspective and the research question.
11. The outcome measurement should result from the outcome identification and this should be straightforward (e.g. if mortality is a main outcome measure this should be taken into account in the analysis). The instrument by which the outcomes are measured should be valid and clearly stated.
12. The method of outcome valuation should be clearly stated. Examples of valuation methods are Discrete Choice Experiments (e.g. Conjoint analysis, Contingent

valuation), Direct utility assessment (VAS, TTO, SG, etc.), Indirect utility assessment (HUI, EQ-5D, QWB, etc.), Person trade off, etc.

13. An incremental analysis should examine the additional costs from one intervention over another, compared to the additional outcomes that it delivers. The incremental costs-effectiveness ratio is obtained by dividing the costs differences (C2-C1) by the outcome differences (O2-O1) for the alternatives.
14. Discounting is done appropriately if all costs and outcomes are converted to one single year, based on a motivated discount rate.
15. All variables in the analysis are potential candidates for the sensitivity analysis. Only variables that are certain or which have a minimal impact on the study results (based on the preliminary analysis) can be excluded from the sensitivity analysis. Furthermore, a justification should be given over the range of the variables used in the sensitivity analysis.
16. Do the authors interpret their results cautiously and are their conclusions justified by the data.
17. This can be done by being explicit about the viewpoint of analysis and by indicating how particular costs and outcomes vary by location, setting, patient population, care provider, etc.
18. If an external agency finances the study, a statement should explicitly be given about who finances the study to guarantee transparency in the relationship between the sponsor and the researcher. Whenever a potential conflict of interest is possible a declaration should be given of 'competing interest'.
19. Does the article notes ethical aspects and elaborates on the characteristics of the population experiencing the disease or the intervention (young, old, poor, wealthy) and how this may have distributional implications.

APPENDIX FILE 7.4 - CHEC SCORES

See the link below:
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10040072/

CHAPTER 8

ADVOCATING UNIFORMITY IN SPINE SURGERY: A PRACTICAL DISEASE-SPECIFIC GUIDELINE FOR TRIAL-BASED ECONOMIC EVALUATIONS

Droeghaag R[*], Schuermans VN[*], Hermans SM, Smeets AY, Caelers IJ, Hiligsmann M, Van Hemert WL, Evers SM, Van Santbrink H
*Both authors contributed equally to this work.

BMJ Open 2023;13(7):e073535

ABSTRACT

Objectives
Despite the availability of general and national guidelines for the conduct and reporting of economic evaluations, there is heterogeneity in economic evolutions concerning spine surgery. This is partly the result of differing levels of adherence to the existing guidelines and the lack of disease-specific recommendations for economic evaluations. The extensive heterogeneity in study design, follow-up duration and outcome measurements limit the comparability of economic evaluations in spine surgery.
This study has three objectives: (1) to create disease-specific recommendations for the design and conduct of trial-based economic-evaluations in spine surgery, (2) to define recommendations for reporting of economic evaluations in spine surgery as a complement to the CHEERS 2022 checklist, (3) to discuss methodological challenges and defining the need for future research.

Design
A modified Delphi method according to the RAND/UCLA Appropriateness Method.

Setting
A four-step process was followed to create and validate disease-specific statements and recommendations for the conduct and reporting of trial-based economic evaluations in spine surgery. Consensus was defined as >75% agreement.

Participants
A total of 20 experts were included in the expert group. Validation of the final recommendations was obtained in a Delphi Panel, which consisted of 40 researchers in the field which were not included in the expert group.

Primary and secondary outcome measures
The primary outcome measure is a set of recommendations for the conduct and reporting, as a complement to the CHEERS 2022 checklist, of economic evaluations in spine surgery.

Results
A total of 31 recommendations are made. The Delphi Panel confirmed consensus on all of the recommendations in the proposed guideline.

Conclusion
This study provides an accessible and practical guideline for the conduct of trial-based economic evaluations in spine surgery. This disease-specific guideline is a complement to existing guidelines, and should aid in reaching uniformity and comparability.

Strengths and limitations of this study

- This is the first available, practical guideline for disease-specific conduct of cost-effectiveness research in spine surgery.
- The use of a modified Delphi method guarantees the support of professionals in this sector, which ensures a larger adherence and internalization of these recommendations.
- Although the expert group included international experts, the majority is from Europe, the guideline might thus reflect European preferences.
- This guideline focuses solely on trial-based economic evaluations.

1. INTRODUCTION

Taking into account ever-increasing healthcare expenses, the importance of economic evaluations is evident. Degenerative pathology is the main driver of costs within spine surgery[1–4]. The burden of degenerative pathology concomitantly increases with aging of the population. To limit the increase of spine surgery-related healthcare costs, scarce healthcare resources should be allocated efficiently. Moreover, spine surgery has a direct influence on patient productivity, and an indirect effect on family and informal caregiver productivity. Hence, proper economic evaluation of surgical procedures is of utmost importance[5,6].

The majority of recently published systematic reviews on economic evaluations in spine surgery conclude that there is abundant heterogeneity and a lack of quality within the field[7–9]. To investigate the extent of this heterogeneity, our group conducted a systematic review that assessed all trial-based economic evaluations in spine surgery as a first step of this Delphi process[10,11]. The aim was to evaluate the methodology and quality of all trial based economic evaluations in spine surgery, which enabled us to identify the disparities in the current practice[10,11].

The results of this broad systematic review show that the importance of economic evaluations is increasingly recognized, as reflected by the increase in the number of cost-effectiveness studies in the last decade[11]. The moderate quality and, more importantly, extensive heterogeneity of these economic evaluations however greatly limit the comparability of their findings. Heterogeneity is caused by variable study designs, follow-up duration and outcome measurements such as utility, effectiveness and costs. Furthermore, studies differ largely in perspectives used, disparities in calculation methods of costs and/or charges, included cost items, different in- and exclusion criteria and baseline characteristics[11]. The results of this systematic literature review provide a foundation for the development of adequate recommendations to increase uniformity in economic evaluations in spine surgery.

Despite the availability of general and national guidelines for the conduct and reporting of economic evaluations, differing levels of adherence result in a wide variety of findings. A disease-specific guideline may provide more appropriate guidance in the conduct and reporting of economic evaluations in spine surgery[12–14]. General guidelines, by nature, do not incorporate disease- and topic-specific recommendations, which may provide insufficient guidance for specific topics. A disease-specific guideline as a supplement to general guidelines is necessary to ameliorate the overall quality and comparability of research[8,15–17]. Several disease-specific guidelines regarding the conduct of economic evaluations are available, but not in the field of spine surgery[18–21].

Therefore, this study has three objectives; (1) To create disease-specific recommendations for the design and conduct of trial-based economic-evaluations in spine surgery, (2) To construct recommendations for reporting of economic evaluations in spine surgery as a complement to the CHEERS 2022 checklist[22] (3) To discuss methodological challenges and defining the need for future research.

2. METHODS

A modified Delphi study was conducted according to the RAND/UCLA Appropriateness Method[23,24]. A four-step process was followed to create and validate disease-specific statements and recommendations for the conduct and reporting of trial-based economic evaluations in spine surgery (Figure 8.1). This study focuses on trial-based economic evaluations specifically. The majority of studies in the field of spine surgery are trial-based, and existing guidelines mainly focus on model-based economic evaluations. The aim is to create a practical guideline for clinical researchers in the field to help fill in the gap of application of trial-based economic evaluations. Authors formed a multi-center expert group consisting of experienced researchers in spine surgery and health economics.

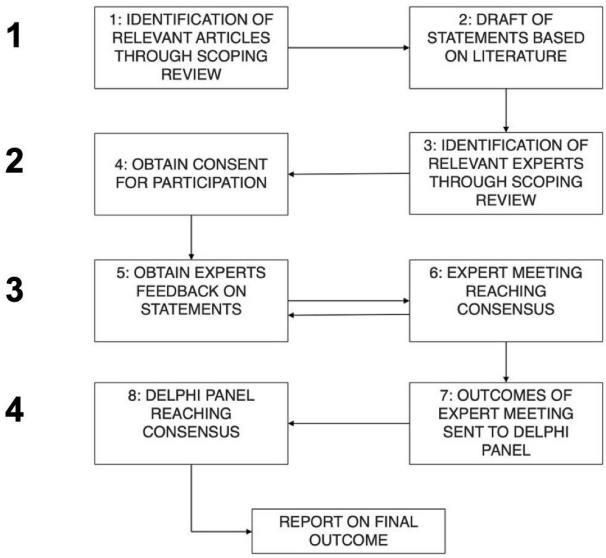

Figure 8.1 - Flowchart of the steps of the modified Delphi process.

2.1. Systematic literature review and identification of experts

A systematic review was conducted in July 2021 to assess general guidelines or recommendations on economic evaluations, and articles concerning economic evaluations in spine surgery. The systematic review was conducted in accordance with the PRISMA statement[25,26]. This will be made available as an Open Access article[11].

2.1.1. Identifying relevant studies

Relevant studies were selected and reviewed based on title and abstract. Articles deemed appropriate for inclusion were reviewed for further analysis. For more details and information, the full-text article can be consulted[11].

2.1.2. Identifying experts and delphi-panel

Formation of the expert group

Specifically first and last authors were identified from included articles derived from the systematic literature search to form the expert group. In addition, economic experts in health economics who contributed to the development of general guidelines and disease specific guidelines were invited to join the expert group as well. To prevent missing relevant experts, the first and last identified authors were asked to propose additional suitable experts to be included. The role of the expert group was to perform a primary validation of statements drafted by the research group. All experts were approached for participation in the expert group through e-mail. This e-mail included a summary of the study design, the objectives and a request for participation. Written consent was obtained from all individual experts before participation. We aimed to include at least 15 experts. To ascertain an organized group discussion, we maintained a group maximum of 30 experts.

Delphi-panel formation

To obtain a broader validation of the recommendations, a Delphi panel was formed with researchers in the field that were not included in the expert group. Whereas the expert group was formed based on the first and last authors of the articles included in the literature review, all identified authors of included articles could be included in the Delphi Panel. Experts were also asked to propose additional colleagues, researchers and residents with experience in the field. The number of participants in the Delphi panel was not limited, a minimum number of 30 participants was required.
Expert group members were excluded from the Delphi-panel. The Delphi Panel was then asked to participate in an online survey.

2.3. Drafting first statements

The research group drafted statements based on the results of the abovementioned systematic literature review[11]. Recommendations were made for, but not limited to, the following topics;

(1) Design and conduct of trial-based economic evaluations.
(2) Reporting of economic evaluations, as a complement to the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist.
(3) Discussion on methodological limitations and define the need for future research.

Full-text articles from the systematic review were analyzed by the authors. The methodological features and limitations were extracted and collected in a spreadsheet divided in the abovementioned topics. All these features were synthesized into meaningful clusters and weighed by frequency and relevance. The first recommendations were drafted based on these findings. These drafts were then revised according to the feedback and input of the senior authors.

2.3.1. Validation by expert group

Online survey

The previously developed statements were sent to the expert group to obtain a level of consensus and feedback. Feedback was received through a web-based questionnaire, built in Google Forms [Appendix Files 8.2]. Demographic and professional characteristics of participants were collected. Level of consensus was assessed on a 0 to 10 scale for each statement, in which 0 meant "disagree", 5 meant "neutral" and 10 means "agree". The experts were asked whether they thought a statement was relevant to be included in the guideline on a scale from 0 to 3, in which 0 meant "not relevant" and 3 meant "relevant". Experts were given the opportunity to provided textual feedback on each statement. Furthermore, all experts could suggest additional statements and were invited to leave further comments or advice for the research group. To prevent discussion between the experts, they were blinded during this stage of the process.

Expert meetings

Subsequently, two expert meetings were held to discuss statements and feedback provided by the expert group. The meetings were organized online with the use of Microsoft Teams [Version 1.5.00.27260]. The expert meetings were led by a member of the research group (VS or RD). Consensus was defined as a score of 75% or higher in terms of agreement in each category. A neutral score was not considered as disagreement. Statements were accepted if consensus was reached by the experts[24,27]. If consensus could not be reached on a proposed statement during the expert meeting, the statement was discarded, adjusted or reformulated. If no consensus could be reached after discussion, the statement was not included in the final guideline. After two expert meetings, consensus was reached on all drafted statements. These final statements were sent out to all participating experts for definitive approval.

2.4. Validation by Delphi panel

The Delphi method is a structured process, commonly used to develop healthcare quality indicators and consists of four key components; iteration, controlled acquisition of feedback, aggregation of responses, and anonymity. We used the term modified as anonymity was not always applicable in our situation [24,28]. As described above, Google Forms was used [Appendix File 8.3], recommendations were adjusted according to the

feedback obtained in the expert meeting. For each recommendation, the Delphi panel could score 'Agree', 'Neutral', 'Disagree', or 'Don't know'.
All consensus statements were gathered and sent to the Delphi panel for final evaluation and validation. Statements reaching consensus of more than 75% were accepted for the final guideline after the 2 expert meetings and validation in the Delphi-panel.

2.5. Final report on outcomes

All consensus statements are reported in this paper, in the form of final recommendations for economic evaluations in spine surgery. Encountered methodological challenges and need for further research are discussed.

2.6. Patients and public involvement

No patients involved.

3. RESULTS

3.1. Drafting of statements

Forty-one statements were drafted by the research group based on the articles included in the systematic review of economic evaluations in spine surgery (N=108) and other relevant literature, including disease-specific or general guidelines (N=28). The initial statements can be found in Appendix File 8.4. Feedback and input from the advisory board resulted in 35 statements remaining for expert group review.

3.2. Expert group

Twenty-five experts who had extensive experience in spine surgery and/or cost-effectiveness research in the field of spine surgery agreed to participate in the expert group, of which 20 actively participated in either the online survey, the expert meeting, or both. The group included experts from Europe (N=14), North America (N=4), Australia (N=1), and Asia (N=1). Seventeen of these experts had a doctorate degree, the remaining three had a University Master's degree. Eleven experts had a background in Health Economics, eight in Medical Science (spine surgeons), and one in Biomedical Engineering. The majority (N=14) of experts have been active in their field for over a decade, and a considerable number of experts have published over 50 articles in the last decade (N=8). All experts reported the use of general, national or regional guidelines in their current practice.

3.3. Validation by expert group

During the first expert feedback round in the online survey, consensus was reached for 20 out of 33 statements (60.6%). Two additional statements (18 & 31) required multiple answers as they concern recommended effectiveness outcome measures to be used; level of agreement (LoA) could thus not be measured for these statements. The LoA after the online survey is summarized in Figure 8.2. All statements were deemed relevant (Figure 8.3). After thorough discussion during the two online expert meetings and adjustments of the statements according to the feedback, consensus was reached on 31 recommendations, including statement 18 and 31.

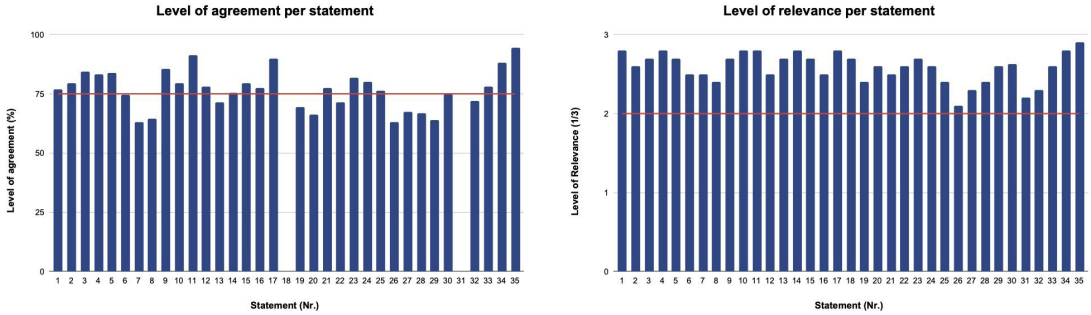

Figure 8.2 - Level of agreement per statement. Percentage (%) of agreement (left). Level of relevance (right) per statement, indicated with a score from 0 (irrelevant) to 3 (extremely relevant). The red line indicates the cut-off for consensus (>75% agreement).

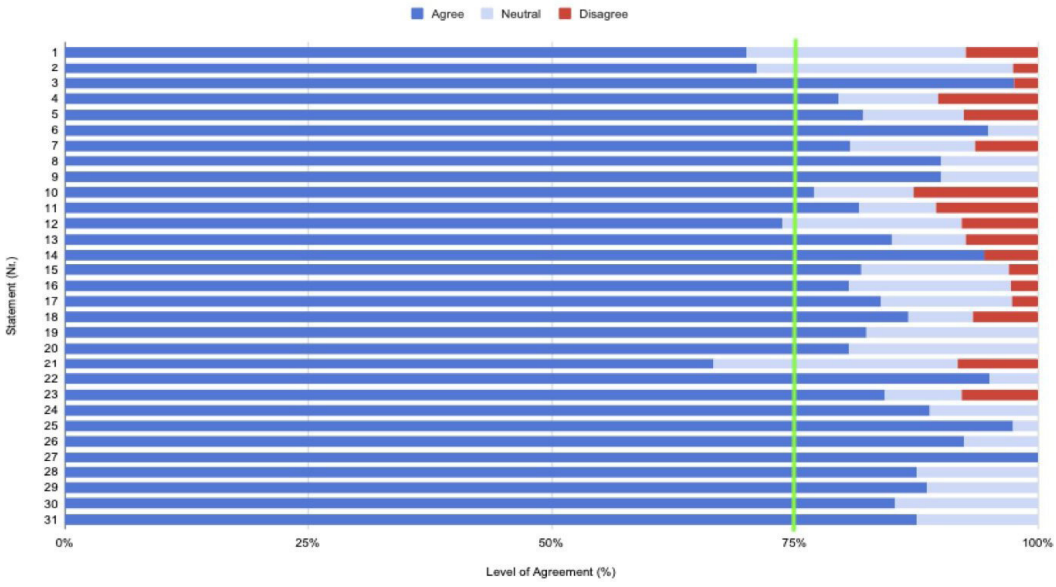

Figure 8.3 - Level of agreement on final statements. Indicated per statement in percentage (%). The green line indicates the cut-off for consensus (>75% agreement).

3.4. Validation by Delphi panel

The 31 recommendations that reached consensus in the expert group were sent out to a larger Delphi panel for final validation. A total of 224 previously identified researchers in the field of spine surgery and/or health economics were invited to validate the recommendations through an online survey. A total of 40 researchers completed the survey. Consensus was reached for all recommendations, none of the recommendations reached more than 25% disagreement. Complete results can be found in Figure 8.3.

3.5. Final recommendations

A comprehensive overview of the final recommendations is provided in Table 8.1.
The main elements of debate in the expert meetings are summarized per statement (#)
(#1) Although generally an RCT is recommended, several experts pointed out that in specific cases, prospective comparative observational studies with very large cohorts are preferable.
(#2) As quality of life is the most important outcome for most spine surgeries, a cost-utility analysis (CUA) is preferred over a CEA. Since CEA investigates a specific clinical outcome of effectiveness, it is often too narrow to capture all relevant outcomes in a comparable fashion. However, in some situations in which a specific clinical outcome is of primary interest, a CEA is an acceptable alternative. We recommend the use of effect measures alongside utility measures in a CUA.
Choosing one preferred utility or effect measure is challenging. Researchers may prefer a specific outcome measure without solid scientific evidence. Choosing one effect or utility measure makes future studies more comparable. The chosen outcome measure in this guideline is the result of an extensive process under experts in the field. Hopefully resulting in consensus amongst future users.
(#5) Controversy remains concerning the definition of the standard of care. For example, the standard of care might differ per population, per country, and over time. Therefore, it is important that the authors describe clearly how the standard of care is defined in the study.
(#7) Since discount rates vary per country or region, it was deemed better not to recommend a specific discount rate. Rather, it is recommended to consult national guidelines for discount rates. An additional analysis using a 0% discount rate is recommended to increase comparability between studies. As performing a sensitivity analysis was not within the scope of this work, it is advised to consult the Professional Society for Health Economics and Outcomes Research (ISPOR) for further reading[29].
(#11) We define complementary therapies in the clinical management pathway as all complementary therapies received both inside and outside of the hospital, as prescribed by the attending physician; e.g., physical or occupational therapy. Costs of these therapies should be included in healthcare costs. All other self-initiated complementary therapies should be accounted for in the community costs when adapting a societal perspective, e.g., physical or occupational therapy, acupuncture, etc.

Table 8.1 - Recommendations for trial-based economic evaluations in spine surgery.

CATEGORY		RECOMMENDATIONS
General		**These recommendations are designed to supplement the existing (inter)national guidelines. If available, these should be consulted. All recommendations are designed for trial-based economic evaluations in spine surgery specifically.**
Conduct	**Study Design**	1. Randomized controlled trials or meta-analyses of RCTs are the gold standard for measuring the effect-size in economic evaluations. If an RCT is not feasible, a prospective study is preferred over a retrospective study, both with a comparative group.
		2. In spine surgery, cost-utility analysis is the preferred method.
		3. The economic evaluation should preferably be performed from both the healthcare and societal perspective.
		4. In spine surgery a minimum follow-up of 2 years is advised for clinical trials. A shorter follow-up period may be acceptable for a specific intervention, only if all costs and effects are expected within the chosen period.
		5. The standard of care should at least be chosen as comparator. If conservative treatment is the standard of care, this should be chosen as a comparator.
		6. An adequate time-horizon should be adapted based on the interventions investigated and should be able to capture most of the relevant costs and benefits over time.
		7. Costs and effects should be discounted if a time horizon longer than one year is used. Sensitivity analyses for different discount rates should be performed, including an analysis with 0% discount rate.
	Outcomes (Costs)	8. Resources should be identified, measured and valued in detail, to ensure that the study can be replicated.
		9. Costs should be further divided into specified categories, that are more descriptive than direct and indirect costs. E.g., healthcare costs, community costs, lost productivity, etc.
		10. In spine surgery, the following categories of costs should be included when adapting a societal perspective; healthcare costs, community costs, lost productivity, patient and family costs. When adapting a healthcare perspective, only healthcare costs should be included.
		11. All therapies of the clinical management pathway should be included in healthcare costs. If a societal perspective is adapted, all complementary therapies should be accounted for in the community costs.
		12. Resource use and medical consumption should be measured using existing databases of prospectively collected data. If such databases are not available or not all relevant resources are covered, patient reported measures can be integrated. Per patient resource data is preferred over the use of accumulated group data (e.g., insurance data).
		13. Actual costs should be used. If costs are not available, tariffs (market prices) should be used.
		14. For the valuation of costs, of market prices, national guidelines or list prices and administrative data regarding hospital costs are recommended.
		15. For loss of productivity, both the friction approach and the human capital approach can be used. The chosen approach should be reported and justified.
		16. Mean national wages are preferred over self-reported wages. Self-reported wages could be used if the investigated population differs from the general population in terms of socio-economic status.
		17. A maximum three-month recall period for questionnaires and patient reported outcomes regarding loss of productivity and resources used is advised. Other recall periods should be justified.
		18. A 'steady state' of the intervention should be assumed, costs should be estimated for routine employment. If relevant and applicable, costs and effects of learning and development could be included and should be reported separately.
		19. If national guidelines are not available, the used discount rate for costs and effects should be justified.

Table 8.1 - (continued)

	Outcomes (Utility & Effect)	1.	Change in quality adjusted life years (QALY) is the most relevant outcome measure for economic evaluations in spine surgery.
		2.	The EQ-5D-5L is the preferred patient reported outcome questionnaire to determine utility outcome (QALY) in spine surgery.
		3.	Even though QALYs are of primary interest in cost-utility analysis in spine surgery, efficacy and safety outcomes (e.g. pain, disability, adverse events) are relevant in most cases and should be assessed [Table 2].
		4.	Lost productivity and informal (unpaid) care should be measured using existing databases of prospectively collected data. If such databases are not available or not all relevant resources are covered, patient reported measures can be integrated.
Reporting		5.	If subpopulations are identifiable and relevant, post-hoc analyses should be performed and reported.
		6.	The used categories of costs should be clearly reported. Costs should be reported separately per category.
		7.	All relevant efficacy and safety outcomes should be reported.
		8.	The reference year used for discounting of costs should be reported.
		9.	If differential discounting is used, the used rates and outcomes should be reported.
		10.	An Incremental Cost-Effectiveness Ratio (ICER) should be calculated and reported in all comparative studies.
		11.	A cost-effectiveness plane can be used to visualize cost-effectiveness.
		12.	A Cost-Effectiveness Acceptability Curve (CEAC) could be used to visualize the impact of willingness to pay for a certain outcome.

(#17) Discussion persists regarding the optimal recall period for patient reported outcome measures[30]. For accuracy, a short interval is preferable. However, for feasibility, longer recall periods are desirable. To optimize accuracy while maintaining feasibility, we recommend a recall period of three months. It should be noted that a recall period of three months does not necessarily mean that the questionnaire interval should also be three months.
(#21) Different questionnaires exist to evaluate QALYs. Several of these questionnaires can be suitable and are used in spine surgery research. As many of the existing studies used the EQ-5D, and as the majority of the experts had a preference for the EQ-5D, we recommend this questionnaire to evaluate QALYs in a uniform fashion.
There was little discussion concerning the recommendations for reporting economic evaluations in spine surgery. Consensus was reached easily for all statements. As our recommendations on reporting in our guideline are complementary to the CHEERS checklist, we highly recommend adhering to this checklist[22].

3.6. Recommended outcome measures in cost-effectiveness analyses

Throughout the expert meetings, experts were asked to suggest clinical outcome measures to be used in cost-effectiveness analyses (CEAs) for different spinal pathologies. We categorized these into 6 domains: general, cervical spine, thoracic spine, lumbar spine, oncology, and deformative pathology. Based on the experts' feedback, we defined a category of highly recommended outcome measures, defined as recommended by more than 50% of the experts. Optional outcomes measures consist of the remaining proposed outcome measures that can be considered when they are of specific interest (Table 8.2).

Table 8.1 - Recommended Outcome Measures for CEAs.

Domain	Highly recommended outcome measures	Optional outcome measures
General	Adverse events, reoperations, complications, VAS/NRS, ODI, COMI	Blood loss, OR time, LoS, HADS, MCS, PCS, Odom Criteria, GPE
Cervical spine	VAS neck/arm, mJOA	NDI
Thoracic spine	mJOA	EMS, Frankel Scale
Lumbar spine	VAS back/leg, RMDQ	-
Oncology	VAS axial pain, KPS, survival	OSRI, Bartels Score, ambulatory status
Deformative pathology	SRS	-

Visual Analogue Scale (VAS), Numeric Rating Scale (NRS), Oswestry Disability Index (ODI), Operation Room (OR), Length of Stay (LoS), Hospital Anxiety and Depression Scale (HADS), Mental Component Summary (MCS), Physical Component Summary (PCS), Global Perceived Effect Score (GPE), Core Outcome Measures Index (COMI), modified Japanese Orthopedic Association (mJOA), Neck Disability Index (NDI), European Myelopathy Scale (EMS), Roland-Morris Disability Questionnaire (RMDQ), Karnofsky Performance Scale (KPS), Oswestry Spine Risk Index (OSRI), Spinal Instability Neoplastic Score (SINS), Scoliosis Research Society (SRS).

4. DISCUSSION

The objective of this international Delphi study was to create evidence-based recommendations to provide guidance to those involved in research trial-based economic evaluations in spine surgery. We successfully engaged a wide community of experts in the field to ensure that the final recommendations reflect participants' opinions, are meaningful, and help bridge existing gaps in practice. This has resulted in a set of 31 recommendations for the design, conduct and reporting of trial-based economic evaluations, as a complement to the existing guidelines. Moreover, we have identified and discussed methodological challenges and the need for future research.

Widespread variations in study possibly result from differing levels of adherence to the existing general guidelines. By defining these disease-specific guidelines we aim to increase adherence and hence standardization in this kind of research. Although partly overlapping with the existing general guidelines, these spine-specific recommendations complement the general guidelines in several ways. First of all, standardization of spine-specific utility, effectivity and cost measures will enlarge the uniformity of the outcome measures in cost-effectiveness research. Additionally, the Delphi method guarantees the support of professionals within this sector, which ensures a larger adherence and internalization of these recommendations.

This spine-specific guideline is more extensive than the general guidelines for cost-effectiveness research. Although several of the statements might seem self-evident to some researchers, we aimed to provide a benchmark for all researchers in the field. This spine surgery-specific guideline for economic evaluations gathers all necessary features, making it accessible and easy to use for clinical researchers. Another important aspect is the awareness of the existence of these guidelines. Through the Delphi approach, both health economic and medical experts are informed of the existence of a disease-specific guideline in this overlapping field. Publication and implementation of this guideline creates an opportunity for unified practice for the benefit of our patients.

The final recommendations are designed to supplement the existing (inter)national guidelines, which should always be consulted. All recommendations are designed for trial-based economic evaluations in spine surgery specifically.

4.1. Strengths & limitations

The most important feedback from the expert group discussions was used to modify the recommendations and is presented in the paper. However, this paper does not incorporate all considerations to reject or support recommendations. Moreover, we only obtained textual feedback from the expert group, but not from the Delphi Panel, as the aim was merely to measure the level of agreement in this group. Similarly, not all experts could attend the same meeting due to time zone differences, which might have influenced the discussions. Although the expert group included international experts, the majority were from Europe.

Our findings help define the few areas of ongoing controversy that can now be investigated with further focused studies. It is debatable whether generic tools, like EQ-5D-5L or SF-36, are optimal for measuring spine related QALYs. The core outcome measures index (COMI) for back was developed with the aim to assess main outcomes of importance for patients with spinal pathology. However, the COMI is not yet validated to quantify changes in QALY and some discussion exist concerning the lack of consideration of mental wellbeing. Development of a spine specific QALY tool could give better insight in spine related quality of life. Since the score is relatively new, we did not find this outcome measure in the existing literature, however, we believe this to be a good effect outcome measure to use. To maintain comparability with other pathologies this should be used alongside generic tools. As this guideline focuses solely on trial-based economic evaluations, the next step would be to provide disease-specific recommendations for model-based economic evaluations in spine surgery. This could provide a standardized, disease-specific reference case and in-depth recommendations for sensitivity analyses. We intended to incorporate live voting to measure consensus at conferences. As a consequence of the COVID-19 pandemic, the majority of conferences were virtual or postponed. Therefore, we opted for an online survey for the Delphi validation.

5. CONCLUSION

This Delphi consensus study provides an accessible and practical guideline for the conduct of trial-based economic evaluations in spine surgery as a complement to existing guidelines. The final guideline includes 31 recommendations on the conduct and reporting of these economic evaluations. This guideline can be used as a checklist that serves as a minimum standard and should aid in reaching uniformity and comparability.

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APPENDIX FILE 8.1 BMJ PROTOCOL GUIDELINE

Droeghaag R, Schuermans VN, Hermans SM, Smeets AY, Caelers IJ, Hiligsmann M, van Hemert WL, Evers S, van Santbrink H
Evidence-based recommendations for economic evaluations in spine surgery: study protocol for a Delphi consensus. BMJ Open 2021;11(12):e052988.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10347447/

APPENDIX FILE 8.2, 8.3 & 8.4

See the link below:
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10347447/

PART IV

SUMMARY, GENERAL DISCUSSION, AND IMPACT PARAGRAPH

CHAPTER 9

SUMMARY AND GENERAL DISCUSSION

SUMMARY

The aims of this thesis were to: I) gain insight into the symptoms, diagnostic methods, diagnosis, and treatment allocation for patients referred to secondary spinal care; II) assess the clinical effectiveness and cost-effectiveness of lumbar interbody fusion surgery; III) explore the methodological quality of studies on economic evaluations in spine surgery, and to provide expert-based recommendations to ameliorate poor study quality and comparability. The general introduction and thesis outline presented in Chapter 1 provide an overview of the available scientific background regarding the aims of this thesis.

Part I - Demographics in spinal care

Chapter 2 evaluated the characteristics, symptoms, diagnosis, and treatment of 4855 patients referred to a specialized secondary spinal healthcare center. Moreover, an in-depth analysis of resource utilization among a representative subgroup of patients (~20%) was performed. The mean age was 58.1 years old; 56% of patients were female, and the mean BMI was 28. In addition, 28% of the patients used opioids. Mean self-reported health status was 53.3 (EuroQol 5D Visual Analogue Scale; EQ-5D-VAS), and pain ranged from 5.8 to 6.7 (Visual Analogue Scale (VAS) neck/back/arm/leg). Additional imaging was received by 67.7% of patients. Surgical treatment was indicated for 4.9% of patients. The majority (83%) of non-surgically treated patients received out-of-hospital treatment; 25% of patients received neither additional imaging nor in-hospital treatment.
We concluded that the vast majority of patients received non-surgical treatments. We observed that ~10% of all patients had acceptable or good questionnaire scores at the time of referral, and received neither in-hospital imaging nor in-hospital treatment.

Part II - Clinical effectiveness and cost-effectiveness of lumbar interbody fusion surgery

Chapter 3 investigated the clinical effectiveness and safety of the transforaminal lumbar interbody fusion (TLIF) compared to the posterior lumbar interbody fusion (PLIF), twelve months postoperatively. In this multicenter randomized controlled trial in five Dutch hospitals, 161 patients with symptomatic single-level degenerative, isthmic, or iatrogenic lumbar spondylolisthesis were randomly allocated to either TLIF or PLIF (1:1). The primary outcome was disability measured with the Oswestry Disability Index (ODI). Per-protocol analysis included 66 patients in each group. In the TLIF group, ODI improved from 46.7 preoperatively to 20.7 one year postoperatively, while in the PLIF group, ODI improved from 46.0 preoperatively to 24.9 one year postoperatively. However, this difference did not reach significance over time ($P=0.28$). Change over time in quality-adjusted life years (QALY), measured using the Short Form Health Survey (SF-36), was significantly different between groups, in favor of TLIF ($P<0.05$). For all other

patient reported outcome measures (PROMs) assessing quality-adjusted life years (EuroQol 5 Dimensions, 5 Levels; EQ-5D-5L), back and leg pain (Visual Analogue Scale; VAS), anxiety and depression (Hospital Anxiety Depression Scale; HADS), a non-significant difference in favor of TLIF was observed twelve months postoperatively. Perioperative blood loss, duration of surgery, duration of hospitalization, and perioperative or postoperative complications did not differ between TLIF and PLIF.

Chapter 4 described a qualitative study assessing the process of lumbar interbody fusion surgery from first referral to postoperative recovery. Data were gathered by means of semi-structured face-to-face interviews with 27 participants, including 11 patients, 7 informal caregivers and 9 healthcare providers. The interview process was audiotaped, transcribed, and analyzed. Overall, participants were satisfied with the current healthcare process in lumbar fusion surgery. However, we found that lack of educational material and guidance during the process led to insecurity about complaints, surgery, and recovery. To improve the process of lumbar interbody fusion and to increase patient satisfaction, healthcare providers should focus on guiding and educating patients and informal caregivers about the pre-operative trajectory, as well as the surgery and the recovery. From the healthcare providers' perspective, the process could be improved by multidisciplinary consultations and a dedicated spine team in the operation room. Although this study focusses on lumbar fusion surgery, results could be translated to other fields of spine surgery and surgery in general.

Chapter 5 evaluated the currently available literature on cost-effectiveness of open transforaminal lumbar interbody fusion (OTLIF) versus minimally invasive transforaminal lumbar interbody fusion (MITLIF) through a systematic review and meta-analysis. A total of 32 studies were included, nine of which compared OTLIF and MITLIF directly. All studies mentioned healthcare perspective costs, and seven mentioned societal perspective costs. Among the five studies that mentioned cost-effectiveness of OTLIF, the values ranged from $47,303/QALY to $218,766/QALY. Cost-effectiveness of MITLIF was estimated to be $121,105/QALY in one study. Both OTLIF and MITLIF appear to be expensive interventions when using a threshold of $50,000/QALY. A meta-analysis of hospital perspective costs showed a significant overall effect in favor of MITLIF, with a mean difference of $2,650. There was great heterogeneity in healthcare and societal perspective costs due to different inclusion and exclusion factors, baseline characteristics, and calculation methods. The overall quality of studies was low. Prospective randomized studies directly comparing cost-effectiveness of OTLIF and MITLIF from both hospital and societal perspectives are needed to obtain a higher level of evidence. Furthermore, more guidance on the design, conduct and reporting of economic evaluations is needed to increase comparability.

Part III - Economic evaluations in spine surgery

Chapter 6 was comprised of a study protocol to formulate expert-based recommendations for the design, conduct, and reporting of economic evaluations in spine surgery. This study protocol described a modified Delphi approach to formulate expert-based recommendations, which included (1) The conduct of a systematic review to identify relevant publications and identify relevant authors, as well as formation of an expert group and a Delphi panel; (2) Drafting of statements based on articles included in the systematic literature review, and validation of the drafted statements by the expert group. Step 2 can be repeated up to three times, during which statements can be discarded and adjusted. Statements with more than 75% agreement will be accepted as consensus statements; (3) Validation of statements by the Delphi panel; (4) Final recommendations.

Chapter 7 systematically reviewed the available literature on cost-effectiveness in spine surgery as part of the abovementioned modified Delphi approach (step 1). A total of 130 economic evaluations were included, 74 of which were retrospective studies. The majority of these studies had a time horizon shorter than two years. Utility measures varied between the EuroQol 5 dimensions and variations of the Short-Form Health Survey. In addition, effect measures varied widely between Visual Analogue Scale for pain, Neck Disability Index, Oswestry Disability Index, reoperation rates and adverse events. All studies included direct costs from a healthcare perspective, and indirect costs were included in 47 studies. Total Consensus Health Economic Criteria scores ranged from 2 to 18, with a mean score of 12.0 over all 130 studies. Notably, the differences in study designs, follow-up duration and outcome measurements impede proper comparison between studies.

Chapter 8 was comprised of a practical disease-specific guideline for trial-based economic evaluations, based on the outcomes study described in Chapter 6. A total of 20 experts were included in the expert group. Validation of the final recommendations was obtained in a Delphi panel, which consisted of 40 researchers in the field who were not included in the expert group. In total, 31 recommendations for the conduct and reporting of economic evaluations in spine surgery were made. The Delphi panel confirmed consensus on all the recommendations in the proposed guideline.

GENERAL DISCUSSION

This thesis consists of three major topics, centered around effective and cost-effective surgical spinal care. This was motivated by the fact that spinal care is constantly developing, and clinicians and researchers are eager to find new ways to enhance outcomes and efficacy. The next paragraphs discuss different strategies and approaches aimed at improving spinal care: 1) Optimizing the pathway to intervention, 2) Optimizing the indication of surgical interventions, 3) Optimizing the surgical technique, 4) Optimizing the patient, and 5) Optimizing economic evaluations in spine surgery.

Optimizing the pathway to intervention

Most patients seeking secondary care for spinal disorders receive conservative treatment. The results of our cohort study show that many of these conservative treatments (e.g., expectative, physical therapy, bracing) are carried out in the primary care setting. It can be argued that a great influence on the sustainability of spinal healthcare is to be expected when one focuses not only on surgical care pathways, but also on the conservative care pathways[1,2]. Thus far, the body of scientific work concerning the cost-effectiveness of conservative treatment for a variety of spinal disorders is limited[3-6]. Moreover, randomized comparative studies on the effectiveness and cost-effectiveness of different conservative treatment approaches are scarce. The available evidence suggests that cognitive behavioral therapy, graded activity, physical therapy, in-patient rehabilitation, pain management education, advice about lifestyle and exercise, massage, osteopathy, and acupuncture are all cost-effective treatments for chronic low back pain. However, it should be noted that many of these interventions only produce modest effects in reducing complaints, and are deemed cost-effective because of the low costs combined with a high willingness-to-pay threshold[7-14]. Even though combining several conservative treatments might increase effectiveness, it does not seem to increase cost-effectiveness[15,16]. Due to the heterogeneity in the investigated conservative treatments, it is impossible to give specific recommendations on their comparative cost-effectiveness. To properly investigate conservative treatments for this complex category of patients, collaboration between specialists, general partitioners, and paramedics is of utmost importance. To prevent unsustainability of spinal care in the coming decades, healthcare providers should take the collective responsibility of investigating the cost-effectiveness of conservative healthcare pathways for different indications and populations. It is essential to provide the best suitable treatment to the right patients, while also taking the costs into account.

As some patients require surgical intervention, improving the process of selecting these patients can likewise contribute to optimization of cost-effectiveness in spinal care. Previous studies that examine revision of classic patient pathways reported promising results. One study investigated the efficacy of 'Primary Care Plus' for spine-related

complaints. In this study, patients that would normally be referred to secondary spinal care received multidisciplinary out-of-hospital consultation with standardized anamnesis, physical examination and diagnostics focused on red flags. Patients with suspected severe pathology were then referred to secondary care. Of all patients consulting Primary Care Plus, only 10% required referral to secondary care. This was beneficial to patients, healthcare providers, and society in general, as it led to a significant reduction of time-to-diagnosis, while also reducing healthcare related costs[17]. Another previously published study from Wilgenbusch et al. found that a coordinated pathway for referral resulted in a reduction of referred patients, and an increase of over 50% of patients requiring surgery compared to the conventional referral process[18]. A more rigorous proposal to reform spinal care has been published by Goetz et al. This is centered around the Primary Spine Practitioner, a highly trained primary care healthcare provider who will coordinate and manage spine care, following evidence-based clinical guidelines. It is suggested that the implementation of this new type of healthcare provider will increase the value of care for patients, while also promoting the cost-effectiveness of care[19]. The hypothesis that a Primary Spine Practitioner might increase the value of care is in line with our findings in Chapter 4 of this thesis. In our qualitative study, we found that the lack of education and guidance during the process between first referral and surgery led to insecurity about complaints, surgery, and recovery. We suggested that healthcare providers should focus on guiding and educating patients and informal caregivers to improve the process of lumbar interbody fusion and to increase patient satisfaction. A highly trained primary care healthcare provider who will coordinate and manage spine care might thus indeed be advantageous from both the perspective of the healthcare provider and the patient.

Optimizing the indication of surgical interventions

When surgical intervention is necessary, choosing the most appropriate treatment will maximize clinical effectiveness and cost-effectiveness. Furthermore, when several treatment options are proven to be equally effective and safe, opting for the most cost-effective treatment will contribute to a more sustainable healthcare system. The indication for lumbar interbody fusion remains debated, as the evidence from previous clinical trials is conflicting. A systematic review showed that decompression alone is as effective as decompression and interbody fusion in patients with lumbar spinal stenosis[20]. Another systematic review found that in the case of spondylolisthesis, decompression with interbody fusion is superior to decompression alone, with similar complication rates[21]. However, a recently published clinical trial concluded that decompression alone is not inferior to decompression and interbody fusion in patients with degenerative spondylolisthesis[22]. Thus far, no consensus has been reached in terms of which option is optimal for the various categories of patients. It is, however, generally accepted that patients suffering from spinal stenosis without spondylolisthesis or deformity do not require interbody fusion surgery. Unnecessary addition of lumbar interbody fusion may increase the risk of complication, such as infections, hardware failure, or adjacent level

disease[23-25]. The exact indication for the addition of interbody fusion to decompression surgery remains unclear. Furthermore, future comparative non-inferiority trials are needed to ameliorate the profiling of patients requiring interbody fusion, as advancements in patient profiling will result in increased effectiveness, safety, and cost-effectiveness of treatments.

Optimizing the surgical technique

In the research on the effectiveness and cost-effectiveness of surgical interventions presented in this thesis, we focused on the posterior lumbar interbody fusion (PLIF), the transforaminal lumbar interbody fusion (TLIF), and the minimally invasive transforaminal lumbar interbody fusion (MITLIF) for lumbar degenerative disease and spondylolisthesis. The indication for PLIF, TLIF and minimally invasive TLIF are very similar, since the general goal of surgery is comparable in all three approaches[26]. As the clinical effectiveness of the interventions is comparable, choosing the most cost-effective alternative thus provides another means of increasing the value for this type of surgical care. A systematic review published by our research group in 2017 found that although TLIF has advantages over PLIF in complication rate, blood loss, and duration of surgery, the clinical outcome after surgery does not differ[27]. It is hypothesized that TLIF might have some benefits compared to PLIF, mainly as a result of less iatrogenic trauma, reflected in the abovementioned parameters. To compare the short- and long-term safety, clinical effectiveness, and cost-effectiveness of PLIF versus TLIF, a study protocol for the LIFT Study – a double-blind, multicenter RCT – was designed and published[28]. The short-term results of this study, which include the safety and effectivity three months following surgery, showed that there were no significant differences in terms of clinical outcomes measured with PROMs. Unlike the results from the review and our retrospective clinical data, we did not find significant differences in terms of blood loss, duration of surgery, length of hospital-stay, or surgical and postoperative complication[29]. Duration of surgery has been evaluated in several previous trials and reviews. No differences were described in the systematic review of Teng et al.[30], while the RCT of Yang et al. revealed a significant difference in duration of surgery (12 minutes) in favor of TLIF[31]. We believe that a difference of 12 minutes is not clinically relevant, but it could be relevant in the cost-effectiveness analysis. It is possible that in patients with lumbar spinal stenosis undergoing TLIF, surgeons might have chosen for a broader decompression, which could have reduced the advantage in duration of surgery of the unilateral approach of TLIF. Insertion of two cages in PLIF (instead of one cage in TLIF) might explain the non-clinically relevant difference of five minutes between groups. Our finding of similarity in blood loss and days of hospitalization between groups could be explained by the use of a midline approach in both groups, which resulted in less difference in muscle dissection and therefore muscle recovery. Another reason for the equal duration of hospitalization is the use of standardized mobilization programs, applied to both groups by physiotherapists in Dutch hospitals. The retrospective study of De Kunder et al.,

performed in our Dutch hospital, also noted no difference in blood loss and days of hospitalization between methods[32].
Since recovery is expected within the first year postoperatively, we chose the one-year mark to assess long-term clinical effectivity. The analysis after one year showed a significant difference in change over time in quality of life in favor of TLIF. We believe this difference might be a result of less iatrogenic damage associated with the technique, leading to a faster recovery and fewer complaints related to local fibrous tissue formation. Although the difference is statistically significant, it was not clinically relevant, as the change did not reach the Minimal Clinically Important Difference (MCID). Remarkably, for all other outcomes including pain, anxiety and depression and disability, a non-significant difference in favor of TLIF was observed twelve months postoperatively.
As the difference in clinical effectivity between PLIF and TLIF is relatively small, a difference in costs might provide a decisive parameter to favor one technique over the other. However, current available research is inconclusive[33]. We did not perform a cost-effectiveness analysis at one year follow-up, as a minimum follow-up of two years is advised based on the existing general guidelines for economic evaluations[34]. This specific period is recommended based on the fact that the health benefits resulting from the intervention, as well as the associated direct and indirect costs, are expected to occur within these two years[35]. Although longer follow-up periods (e.g., five years, ten years, or lifetime) might result in even more reliable outcomes, the added benefit of these longer follow-up periods are disproportionate and therefore not deemed feasible. The results on cost-effectiveness will thus be analyzed and published after a two-year follow-up is completed.

In order to address the high morbidity in spine surgery, lesser and minimally invasive techniques have been developed in the last decades[36]. Initially, successful implementation of minimally invasive approaches was limited to the less complex interventions such as discectomies or percutaneous screw fixation. The technological advancements in healthcare, e.g., intraoperative imaging, instrumentation, and robot-guided surgery, helped expand the use of minimally invasive surgery to more complex interventions, such as TLIF and PLIF[37]. Previous systematic reviews on the cost-effectiveness of minimally invasive spine surgery indicate that the minimally invasive approaches are indeed more cost-effective than their open counterparts, hence our interest in minimally invasive lumbar fusion surgery grew[38,39]. To compare the cost-effectiveness of the open TLIF (OTLIF) with the minimally invasive TLIF (MITLIF), we conducted a systematic review and meta-analysis. We chose to compare the open and minimally invasive TLIF, instead of the open and minimally invasive PLIF, because TLIF was expected to be non-inferior to PLIF in terms of effectiveness and superior in terms of cost-effectiveness. Even though high-quality
randomized trials directly comparing cost-effectiveness of OTLIF and MITLIF are lacking, the outcomes of this review suggest that MITLIF is more cost-effective than

OTLIF in patients with degenerative disease or spondylolisthesis. This difference is mainly the result of the shorter recovery period, leading to shorter hospital stay and reduced absenteeism associated with MITLIF, and ultimately lower costs. To definitively conclude whether MITLIF is more cost-effective, our research group intends to perform an RCT directly comparing cost-effectiveness of OTLIF and MITLIF from both hospital and societal perspectives. This study will be conducted in accordance with the evidence-based and expert validated guidelines for economic evaluations in spine surgery, as presented in this thesis.

Optimizing the patient

An alternative strategy for improving the effectiveness of lumbar fusion surgery is to positively influence patient-specific characteristics on an individual level. One of these characteristics is physical performance prior to surgery. In a recently published thesis on healthcare pathway optimization, the influence of physical performance on outcomes after lumbar fusion surgery were investigated[40]. Based on retrospective data, it was apparent that physical performance measures such as movement control, back muscle endurance strength and extensor strength, aerobic capacity and flexibility were associated with short- and long-term outcomes after surgery[41]. A subsequent pilot study on the effectiveness and feasibility of pre-operative high-intensity interval training to positively influence surgical outcomes was conducted. This study confirmed that exercise-based pre-habilitation is a safe and effective way to improve the time to functional recovery after surgery[42]. Similar beneficial effects of exercise-based pre-habilitation were found in another study by Nielsen et al.[43]. Besides this finding, they also concluded that their pre-habilitation program was more cost-effective compared to the standard care[44].

The interest in the biopsychosocial model in surgical spinal care has been rising over the last decades[45]. Consequently, interest in intervention regarding the psychological aspects in spine surgery has also spiked. Perhaps the most investigated intervention in this category is cognitive behavioral therapy (CBT)[46]. CBT is mostly used as a form of pre-habilitation. The number of studies on the topic has been steadily increasing over recent years. A recent systematic review suggests that pre-habilitation in the form of CBT will result in significantly better surgical outcomes, but mainly in selected populations[47,48]. To investigate whether CBT might be of added value for a selected group of patients undergoing lumbar interbody fusion, our research group is currently conducting an international randomized controlled trial comparing the effect of CBT to perioperative education in patients that catastrophize pain[49].

Optimizing economic evaluations in spine surgery

While conducting systematic reviews on varying topics regarding the cost-effectiveness of surgical interventions to the spine, our research group found great heterogeneity in design, conduct and reporting across different topics[33,50-52]. In most instances, the striking

heterogeneity made comparison of results from different studies impossible. Interestingly, other authors of systematic reviews in the field of spine surgery found similar results, and many concluded that more guidance was needed to improve quality and comparability[53-55].

To evaluate whether this heterogeneity was present within the entire scientific field of economic evaluations in spine surgery, we conducted a systematic review to assess the methodology and quality of these studies. The findings of this study enabled us to critically assess our own work, and served as a basis for the development of evidence-based recommendations for economic evaluation in the field of spine surgery in the form of a practical guideline. As experts from different countries from around the globe were actively involved in the creation of these recommendations, and later in the validation of the guideline, the work encompasses considerations that would otherwise not have been explored or incorporated. The implications of this work will not only ameliorate the future work by our own research team, but will hopefully lead to improved quality of research in the entire field of spine surgery. Moreover, it raises awareness for the important topic of cost-effectiveness research, and promotes comparability of future studies. Another positive effect of the publication of the detailed study protocol, systematic qualitative assessment, and final guideline is the fact that our work could serve as a blueprint for the development of other disease-specific guidelines in orthopaedic surgery and neurosurgery.

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CHAPTER 10

IMPACT PARAGRAPH

IMPACT PARAGRAPH

The main objective of the scientific work described in this thesis is to increase the effectiveness and cost-effectiveness of spine surgery in general, and of lumbar interbody fusion surgery in particular.

In **Part I**, we found that the vast majority of patients referred to secondary healthcare for spine-related problems did not require specialized in-hospital treatment. Only a select group of patients was treated surgically. Although we found several significant differences in characteristics between groups of patients receiving different treatments, no variables were sufficiently specific enough to aid in patient profiling. The outcomes of our study suggest that there is relevant potential for improving the efficacy of referral, diagnosis, and treatment, for example by triaging referrals, educating referring doctors, and organizing multidisciplinary out-of-hospital consultation. However, the current lack of knowledge on the effectiveness of healthcare pathways for different categories of patients impedes further healthcare optimization. The detailed analysis in our study provides a scientific basis to further investigate the relationship between patient characteristics and effectiveness of new healthcare pathways, including non-surgical treatments. Improving spinal care will benefit a large group of patients, as spinal disorders are amongst the conditions with the highest burden of disease worldwide – and this is expected to rise in the future. Optimizing the patient-journey from first referral to diagnosis and treatment has several major impacts. Firstly, referring the patient to the right (para)medic (i.e., physical therapist, neurologist, orthopedic surgeon) reduces waiting times and thus results in shorter time to diagnosis and treatment. Secondly, improved patient profiling will lead to better treatment allocation, improving the effectiveness of a treatment. Lastly, optimizing the patient-journey from referral to treatment will lead to a reduction in associated costs.

Part II was comprised of studies focused on clinical effectiveness and cost-effectiveness of lumbar interbody fusion surgery. In these studies, we compared different surgical techniques that are commonly accepted and performed to alleviate neurological complaints by decompressing neurological structures and achieving interbody fusion. The choice of technique is still mainly based on surgeons' preferences and availability. We found that one of the techniques – the transforaminal lumber interbody fusion (TLIF) – is not inferior in increasing quality of life compared to its competitor, the posterior lumbar interbody fusion (PLIF). This difference in clinical effectiveness might result in increased cost-effectiveness. An economic evaluation study using the two-year follow-up data of the randomized controlled trial comparing both techniques will be performed in the near future, providing a definitive answer to the question of whether one technique is favorable over the other.
We also found that the minimally invasive TLIF (MITLIF) might be more cost-effective compared to the traditional open approach. The apparent benefits of the MITLIF include

faster recovery and better short- and long-term outcomes, in turn resulting in lower (indirect) costs, for example by reducing loss of productivity. Although the MITLIF seems promising, evidence from well-powered prospective studies is lacking. To address this knowledge gap, our research team initiated a well-powered randomized controlled trial comparing both techniques. We expect to publish the protocol for this study in the coming year. The outcomes of our randomized controlled trials on cost-effectiveness will be used in a budget impact analysis (BIA), which is a specific assessment to evaluate the impact of implementing an intervention on healthcare costs. The results of a BIA are not only of interest to clinicians, but also to policymakers and healthcare insurance companies.

In addition to quantitative research, this thesis includes a qualitative analysis on the process of lumbar interbody fusion from the perspective of patients, informal caregivers, and healthcare providers. Overall, participants were satisfied with the current healthcare-process in lumbar fusion surgery. However, we found that relatively small changes in the patient-journey (e.g., educational material, guidance during the process) could increase satisfaction. Although this study focusses on lumbar fusion surgery, results could be translated to other fields of spine surgery.

The findings in Part II have a direct impact on care delivered to patients, both regionally and globally. Moreover, choosing the most cost-effective treatment is of great importance considering the increase in healthcare costs of instrumented spine surgery worldwide.

Lastly, **Part III** addressed an important knowledge gap in the scientific community of spine surgery. During our research on cost-effectiveness, we concluded that despite the availability of general and national guidelines for the conduct and reporting of economic evaluations, there is heterogeneity in economic evaluations concerning spine surgery. This is partly the result of different levels of adherence to the existing guidelines, possibly due to lack of awareness, as well as the lack of disease-specific recommendations for economic evaluations. The extensive heterogeneity in study design, follow-up duration and outcome measurements limits the comparability of economic evaluations in spine surgery. To address this problem, we created an accessible and practical disease-specific guideline for the design and conduct of trial-based economic evaluations in spine surgery. This disease-specific guideline is a complement to existing guidelines and should aid in reaching uniformity and comparability. As experts from all over the world were involved in the creation of this guideline, strong adherence and internalization of the recommendation is expected.

The anticipated increase in study quality and comparability will reduce the need for country- or region-specific studies and will thus result in fewer studies needed to gain definitive insight on the economic value of interventions. Ultimately, this could accelerate value-based healthcare in spine surgery on a global scale.

CHAPTER 11

SAMENVATTING

SAMENVATTING

De doelstellingen van dit proefschrift waren: I) inzicht verkrijgen in de symptomen, diagnostische methoden, diagnose en gekozen behandeling voor patiënten verwezen naar secundaire wervelkolomzorg; II) de klinische effectiviteit en kosteneffectiviteit van lumbale intercorporele fusiechirurgie beoordelen; III) de kwaliteit van studies over economische evaluaties in wervelkolomchirurgie onderzoeken en op de mening van experts gebaseerde aanbevelingen doen om de kwaliteit en vergelijkbaarheid van studies te verbeteren. De algemene inleiding en de omschrijving van de inhoud van de thesis in Hoofdstuk 1 geven een overzicht van de beschikbare wetenschappelijke achtergrond met betrekking tot de doelstellingen van dit proefschrift.

Deel I - Demografie binnen de wervelkolomzorg

Hoofdstuk 2 beschrijft de kenmerken, symptomen, diagnoses en behandelingen van 4855 patiënten doorverwezen naar een gespecialiseerd secundair centrum voor wervelkolomzorg. Ook werd een analyse van het gebruik van middelen uitgevoerd bij een representatieve subgroep van patiënten (~20%). De gemiddelde leeftijd was 58,1 jaar, 56% van de patiënten was vrouw en de gemiddelde BMI was 28. Bovendien gebruikte 28% van de patiënten morfine-achtige pijnstillers (opioïden). De gemiddelde door de patiënt gerapporteerde gezondheidstoestand was 53,3 (EuroQol 5D Visuele Analoge Schaal (EQ-5D-VAS)), en de pijn varieerde van 5,8 tot 6,7 (Visuele Analoge Schaal (VAS) nek/rug/arm/been)). 67,7% van de patiënten kreeg aanvullend beeldvormend onderzoek. Er werd bij 4.9% van de patiënten gekozen voor chirurgische behandeling. De meerderheid (83%) van de niet-chirurgisch behandelde patiënten kreeg een behandeling buiten het ziekenhuis; 25% van de patiënten kreeg noch aanvullende beeldvorming noch een behandeling in het ziekenhuis.

We concludeerden dat de overgrote meerderheid van de patiënten niet-chirurgische behandelingen kreeg. We observeerden dat ~10% van alle patiënten acceptabele of goede vragenlijstscores had op het moment van verwijzing en noch aanvullende beeldvorming noch een behandeling in het ziekenhuis kreeg.

Deel II - Klinische effectiviteit en kosteneffectiviteit van lumbale intercorporele fusiechirurgie

Hoofdstuk 3 omvat een onderzoek naar de klinische effectiviteit en veiligheid van de transforaminale lumbale intercorporele fusie (TLIF) ten opzichte van de posterieure lumbale intercorporele fusie (PLIF), twaalf maanden na de operatie. In dit multicenter gerandomiseerde gecontroleerde onderzoek in vijf Nederlandse ziekenhuizen werden 161 patiënten met symptomatische degeneratieve, lytische, of iatrogene lumbale

spondylolisthesis op één niveau gerandomiseerd tussen TLIF of PLIF. Het primaire resultaat was invaliditeit gemeten met de Oswestry Disability Index (ODI). Er werden 66 patiënten per groep meegenomen in de per-protocolanalyse. In de TLIF-groep verbeterde de ODI van 46,7 preoperatief naar 20,7 een jaar postoperatief. In de PLIF-groep verbeterde de ODI van 46,0 preoperatief naar 24,9. Dit verschil was niet statistisch significant (P=0.28). We observeerden een statistisch significant verschil in verschil in de loop van de tijd in kwaliteit van leven (quality-adjusted life years (QALY)), gemeten met de Short Form Health Survey (SF-36) ten gunste van TLIF (P<0.05). Voor alle andere door patiënten gerapporteerde uitkomstmaten die de kwaliteit van leven (QALY, EuroQol 5 Dimensies, 5 Niveaus (EQ-5D-5L)), rug- en beenpijn (Visuele Analoge Schaal (VAS)), angst en depressie (Hospital Anxiety Depression Scale (HADS)) beoordelen, werden geen statistisch significant verschillen waargenomen. Er was geen verschil in perioperatief bloedverlies, duur van de operatie, duur van ziekenhuisopname, en perioperatieve of postoperatieve complicaties tussen TLIF en PLIF.

Hoofdstuk 4 beschrijft een kwalitatief onderzoek naar het proces van lumbale intercorporele fusiechirurgie vanaf de eerste verwijzing tot aan het postoperatieve herstel. Gegevens werden verzameld door middel van semigestructureerde interviews met 27 deelnemers, waaronder 11 patiënten, 7 mantelzorgers, en 9 zorgverleners. De interviews werden opgenomen, uitgeschreven en geanalyseerd. Over het algemeen waren de deelnemers tevreden over het huidige zorgproces. We concludeerden echter dat een gebrek aan informatief en educatief materiaal en begeleiding tijdens het proces leidde tot onzekerheid over klachten, de operatie en het herstel. Om het proces rondom deze zorg te verbeteren en de tevredenheid van patiënten te vergroten, zouden zorgverleners zich meer moeten richten op het begeleiden en voorlichten van patiënten en mantelzorgers. Vanuit het perspectief van de zorgverleners zou het proces verbeterd kunnen worden door een multidisciplinaire aanpak en een toegewijd operatieteam voor wervelkolomchirurgie. Hoewel dit onderzoek zich richt op lumbale intercorporele fusiechirurgie, kunnen de resultaten worden vertaald naar andere gebieden van wervelkolomchirurgie en chirurgie in het algemeen.

Hoofdstuk 5 beschrijft een systematische beoordeling van de beschikbare literatuur over kosteneffectiviteit van open transforaminale lumbale intercorporele fusie (OTLIF) versus minimaal invasieve transforaminale lumbale intercorporele fusie (MITLIF) door middel van een systematische review en meta-analyse. 32 studies werden geïncludeerd, waarvan negen studies OTLIF en MITLIF direct vergeleken. Alle studies vermeldden kosten vanuit het gezondheidszorgperspectief. Zeven studies vermeldden ook kosten vanuit het sociaalmaatschappelijk perspectief. De kosteneffectiviteit van OTLIF werd vermeld in vijf studies, variërend van $47,303/QALY tot $218,766/QALY. De kosteneffectiviteit van MITLIF werd vermeld in één studie, $121,105/QALY. Zowel OTLIF als MITLIF lijken dure interventies te zijn bij het hanteren van een kosteneffectiviteitsgrens van $50,000/QALY. De meta-analyse van de kosten vanuit het gezondheidszorgperspectief

toonde een significant effect ten gunste van MITLIF, met een gemiddeld verschil van $2,650. Er was grote heterogeniteit in de kosten vanuit het gezondheidszorgperspectief en het sociaalmaatschappelijk perspectief als gevolg van verschillende in- en exclusiefactoren, patiëntkarakteristieken, en berekeningsmethoden. Over het algemeen was de kwaliteit van de studies laag. Prospectieve gerandomiseerde studies die de kosteneffectiviteit van OTLIF en MITLIF direct vergelijken vanuit zowel het perspectief van de gezondheidszorg als het sociaalmaatschappelijk perspectief zijn nodig om een hoger niveau van bewijs te verkrijgen. Bovendien zijn er ziekte-specifieke richtlijnen nodig voor het ontwerp, de uitvoering en rapportage van economische evaluaties om de vergelijkbaarheid te vergroten.

Deel III - Economische evaluaties in de wervelkolomchirurgie

Hoofdstuk 6 omvat een onderzoeksprotocol om op de mening van experts gebaseerde aanbevelingen te formuleren voor het ontwerp, de uitvoering en rapportage van economische evaluaties in wervelkolomchirurgie. Dit onderzoeksprotocol beschreef een gemodificeerde Delphi-studie bestaande uit: (1) Uitvoeren van een systematische review om relevante publicaties auteurs te identificeren en het vormen van een expertgroep en een Delphi-panel. (2) Opstellen van stellingen op basis van bevindingen van de systematische review en validering van opgestelde aanbevelingen door de expertgroep. Stap 2 kan tot drie keer herhaald worden. Aanbevelingen kunnen in deze rondes worden verworpen of aangepast. Aanbevelingen met meer dan 75% consensus worden geaccepteerd. (3) Validering van aanbevelingen door het Delphi-panel. (4) Definitieve aanbevelingen.

Hoofdstuk 7 omvat een systematische beoordeling van de beschikbare literatuur over kosteneffectiviteit in wervelkolomchirurgie als onderdeel van de eerdergenoemde Delphi-studie (stap 1). 130 economische evaluaties werden opgenomen. 74 van deze studies waren retrospectieve studies. De meerderheid van de studies had een tijdshorizon korter dan 2 jaar. Uitkomstmaten over kwaliteit van leven varieerden tussen de EuroQol 5 Dimensies (EQ-5D) en variaties van de Short Form (SF). Effectmaten varieerden tussen de Visuele Analoge Schaal (VAS) voor pijn, Neck Disability Index (NDI), Oswestry Disability Index (ODI), her-operaties en complicaties. Alle studies rapporteerden directe kosten vanuit een gezondheidszorgperspectief. Indirecte kosten werden opgenomen in 47 studies. De totale Consensus Health Economic Criteria (CHEC) scores varieerden van 2 tot 18, met een gemiddelde score van 12,0 over alle 130 studies. De verschillen in onderzoeksopzet, duur van follow-up en gekozen uitkomstmaten belemmeren het onderling vergelijken van studies.

Hoofdstuk 8 beschrijft een praktische ziekte-specifieke richtlijn voor op klinisch onderzoek gebaseerde economische evaluaties. De expertgroep bestond uit 20 mensen. Validering van de definitieve aanbevelingen werd verkregen in een Delphi-panel, bestaande uit 40 onderzoekers in het veld die niet deelnamen in de expertgroep. In totaal

werden 31 aanbevelingen gedaan voor de uitvoering en rapportage van economische evaluaties in de wervelkolomchirurgie. Voor alle aanbevelingen werd consensus bereikt in het Delphi-panel.

CHAPTER 12

DANKWOORD

DANKWOORD

Aan de totstandkoming van dit proefschrift hebben veel mensen op verschillende manieren bijgedragen. Zonder hun hulp was het mij nooit gelukt mijn promotieonderzoek op deze manier af te ronden.

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Geachte copromotor, dr. Van Hemert, beste Wouter,
Onze eerste ontmoeting staat mij goed bij. Toen we elkaar voor het eerst spraken over het onderzoek binnen de wervelkolomchirurgie, wist ik nog niet goed wat ik wilde. Als ik terugkijk op de afgelopen jaren, kan ik concluderen dat ik veel geluk heb gehad met de keuze die ik gemaakt heb. Jij hebt mij gesteund in het onderzoek en hebt veel mogelijk gemaakt. Ook buiten de wetenschap kon ik bij jou terecht voor advies en begeleiding. Jij bent, samen met Henk, een grote inspiratiebron in mijn beginnende carrière. Ik hoop en verwacht dat ik in de toekomst nog veel met je samen mag werken en van je kan leren.

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CHAPTER 13

CURRICULUM VITAE
LIST OF PUBLICATIONS

CURRICULIM VITAE

Ruud Droeghaag was born in Brunssum, The Netherlands, on October 11th, 1996. He is the second child of Ron and Nicole, and brother of Julie and Sophie. He graduated from secondary school (Sint-Janscollege, Hoensbroek) in 2015, with specialization Nature, Health, & Physics. After graduating, Ruud studied Medicine at Maastricht University. During the last years of the study, he started as a student-researcher in spine surgery at the Department of Orthopaedic Surgery, Zuyderland Medical Centre Heerlen-Sittard-Geleen, and the Department of Neurosurgery, Maastricht University Medical Center under supervision of prof. dr. Henk van Santbrink, dr. Wouter van Hemert, and dr. Inge Caelers. During the clinical rotation, Ruuds interest in orthopaedic surgery grew, which led to a senior scientific and clinical internship at the Department of Orthopaedic Surgery in Zuyderland Medical Centre.

After graduating in Medicine in 2021, he began working as a part-time formal PhD candidate in spine surgery under the supervision of prof. dr. Henk van Santbrink, dr. Wouter van Hemert, and dr. Inge Caelers, which resulted in this thesis. Simultaneously, he worked as a part-time resident not in training at the Department of Orthopaedic Surgery in Zuyderland Medical Centre.

Ruud was accepted as resident in training in orthopaedic surgery in ROGO Zuid in 2022. During the last four months of 2022, he worked as a resident not in training at the Intensive Care Unit in Zuyderland Medical Centre. In 2023, Ruud started his specialist orthopaedic training at the Department of Surgery in Zuyderland Medical Centre under supervision of dr. Meindert Sosef, dr. Raoul van Vugt, and drs. Evelien de Witte. In 2024 he will continue his residency at the Department of Orthopaedic Surgery in Zuyderland Medical Centre under supervision of dr. Edwin Jansen and dr. Emil van Haaren.

Besides his medical career, Ruud enjoys being around family and friends, is involved in strength training multiple times a week, and runs an online business with a close friend. He lives together with his partner Jella van de Laak in Geulle, the Netherlands.

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