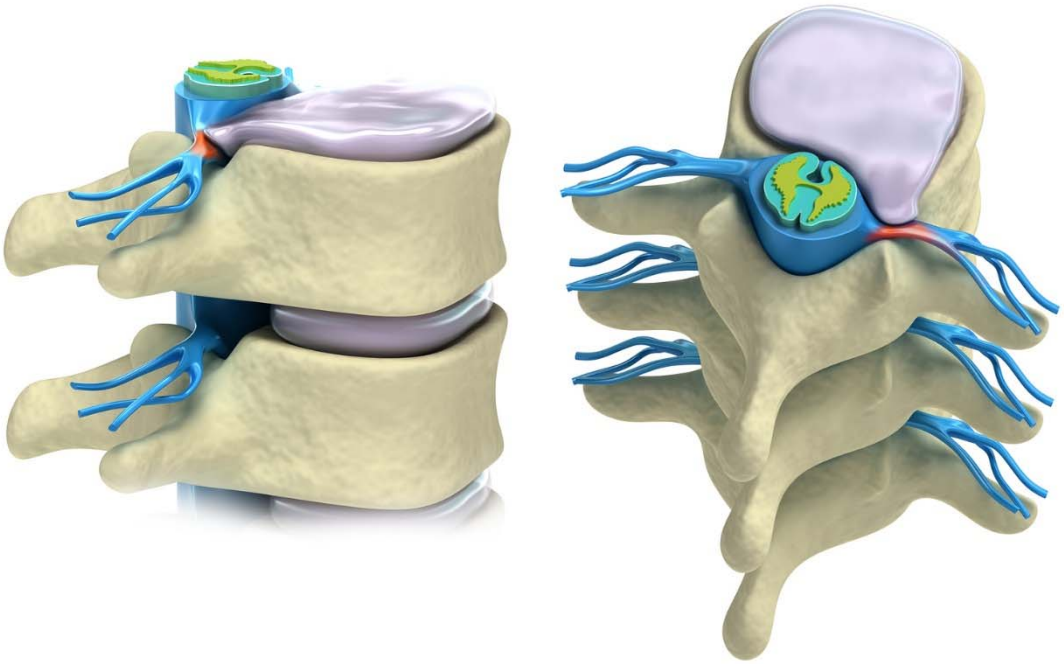
Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
Belgian Health Care Knowledge Centre

SYNTHESIS

CERVICAL AND LUMBAR TOTAL DISC REPLACEMENTS



KCE REPORT 254Cs
HEALTH TECHNOLOGY ASSESSMENT

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SYNTHESIS

CERVICAL AND LUMBAR TOTAL DISC REPLACEMENTS

KIRSTEN HOLDT HENNINGSEN, NANCY THIRY, CHRIS DE LAET, SABINE STORDEUR, CÉCILE CAMBERLIN

FOREWORD

Back pain in general belongs to the most frequent health problems and is responsible for a substantial share of work disability. Is this the price that our species has to pay for having dared to stand upright barely seven millions years ago? Has our head, while *Homo erectus* was becoming *Homo sapiens,* started to weigh too much on this spine that did not have the time yet to get used to the upright position? Whatever the answer may be, with his hands henceforth freed to create tools and with his oversized brain, modern man relentlessly tries to invent new technological fixes to his physical ailments.

Medical industry indeed continuously brings innovative devices on the market, developed in collaboration with clinicians, in an attempt to enrich our therapeutic arsenal. In these two reports published simultaneously, we assessed two technological approaches likely to 'repair' failing backs: firstly the vertebroplasties by means of cement injection in a fractured and compressed (generally lumbar) vertebra, possibly preceded by a re-expansion by a balloon (or balloon kyphoplasty); and secondly the intervertebral disc replacement prostheses.

These new approaches are based on logical thinking and seem to promise new avenues in the notoriously delicate spine surgery. But in fact, do these innovations actually deliver what they promise? More precisely, do the statistically significant results observed in some studies also reflect clinically tangible improvements? In this field eminently subject to psychosomatic influences, do the studies succeed in neutralizing the powerful placebo effect a surgical procedure may engender? And, finally, are the observed results confirmed on the long term? Whoever decides to take a closer look should better be prepared for some surprising results.

Obviously, considering the current context of savings, only innovations with a real and observable added value should be reimbursed. It is a matter of separating the wheat from the chaff, not only to save the scarce health insurance resources for genuinely effective therapies but also to prevent patients from feeding false hopes.

We are thankful to the experts and practicing clinicians who have accompanied us in the development of these two reports, and, by doing so, have contributed, together with us, to an ever more *evidence-based* health insurance.

Christian LÉONARD
Deputy general director

Raf MERTENS
General director

ABSTRACT

OBJECTIVES

To conduct a rapid review to evaluate the clinical effectiveness, safety and cost-effectiveness of cervical and lumbar total disc replacements versus conservative treatment and/or (discectomy and) fusion, respectively in subacute/chronic radicular arm pain and in chronic lumbar pain due to intervertebral disc disorder.

METHODS

Systematic literature review of randomised controlled trials, systematic reviews and full economic evaluations in Medline, Embase, Cochrane and CRD (CDSR, DARE, HTA, NHS EED and CENTRAL). Analysis of national administrative databases and industry-launched survey results.

RESULTS

Although some outcomes were statistically significant, none of the mean differences between cervical total disc replacement and cervical fusion for the main outcomes (quality of life, pain and functional status) were clinically relevant. Similar conclusions apply for the comparison between lumbar total disc replacement and lumbar fusion or conservative treatment. Revision surgery rate was slightly lower after cervical total disc replacement than after cervical fusion but the revision complexity was not taken into account. The results of the (low quality) economic evaluations were divergent, whatever the location of the total disc replacement.

CONCLUSIONS

More large randomised controlled trials including a long follow-up are needed to study the clinical effectiveness and the safety. In the meantime, good quality economic evaluations cannot be performed. There is currently not sufficient evidence to advocate the reimbursement of any of the two artificial discs without strict conditions.

LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
CTDR	Cervical total disc replacement
EQ-5D	EuroQoL 5 dimensions
LTDR	Lumbar total disc replacement
NDI	Neck Disability Index
NRS	Numeric Rating Scale
ODI	Oswestry Disability Index
RCT	Randomised controlled trial
SF-36	Medical Outcome Study Short Form 36-Item Health Survey
TDR	Total disc replacement
VAS	Visual Analog Scale

SYNTHESIS

1. INTRODUCTION

Chronic pain linked to spinal conditions is unfortunately commonly experienced in the general population. In Belgium, one adult out of five declared in 2013 having suffered from low back disorder or other chronic back defect in the previous 12 months, and one out of eight from neck disorder or other chronic neck defect in the same period.[1] Separating adjacent vertebrae, intervertebral discs absorb shocks and offer mobility and stability to the spine. Chronic low back and neck pain as well as radiating leg or arm pain, or neurological dysfunctions can be the consequences of intervertebral disc affection. The narrowing of the space where the spinal cord and the nerves are located, due to a disc hernia or a degenerative disc disease, can cause myelopathy when the spinal cord is compressed and (more frequently) radiculopathy when the nerve roots are compressed.

When the patient does not respond to the conservative arsenal (physical rehabilitation, drugs administration, nerve root injections…), surgery may be considered. Technical variants exist but basically the fusion of vertebrae is a surgical technique during which the pressure on the spinal nerve roots or cord is relieved (decompression), the disc between the vertebrae is generally removed (discectomy) and the two adjacent vertebrae are fastened together, using a bone graft and material such as screws, pedicles or cages. While fusing two vertebrae suppresses the mobility of the spine at the level operated, replacing the damaged natural intervertebral disc by an artificial disc is proposed as an alternative. The artificial disc offers some mobility that supposedly reduces the adjacent level disease incidence by reducing loads on adjacent segments. The cervical total disc replacement represents an alternative to cervical fusion in patients suffering from radicular arm pain. The lumbar prosthesis is an alternative to lumbar fusion in patients suffering from a chronic low back pain due to a degenerative lumbar disc disease.

Total disc replacement in Belgium

According to our analysis of administrative databases and a survey launched by the industry, between 500 and 600 cervical artificial discs and almost 200 lumbar artificial discs are implanted each year in our country.

These total disc replacements are performed by orthopaedic surgeons or neurosurgeons. Patients stay a few days at the hospital. They are women and men (to a slightly lesser extent) in their forties.

The implantation intervention is reimbursed but currently only the lumbar disc prosthesis is reimbursed (€1800) with in addition a maximum cost of €180 for the patient. The cost of a cervical prosthesis (around €2500) is fully borne by the patient.

2. AIM AND SCOPE

In 2006, a first KCE report[2] was published, covering the lumbar total disc replacement (LTDR). The evidence was so scarce on cervical total disc replacement (CTDR) at that point in time that this topic was not considered in the review. Almost ten years after, the clinical evidence has evolved for both LTDR and CTDR, and an update on the topic was thus timely.

The aim of the present study is to answer the following research questions:

1. What is the evidence of the short-term and long-term clinical effectiveness, safety and cost-effectiveness of CTDR versus conservative treatment and/or (discectomy and) fusion in subacute/chronic[a] radicular arm pain?
2. What is the evidence of the short-term and long-term clinical effectiveness, safety and cost-effectiveness of LTDR versus conservative treatment and/or (discectomy and) fusion in chronic lumbar pain due to intervertebral disc disorder?

Partial disc replacements and (even scarcer) thoracic prostheses are not covered. Organisational, legal, ethical or patient issues other than patient outcomes (patient satisfaction, quality of life) are not addressed in the present report.

[a] In the present study we considered a pain as subacute if lasting more than 6 weeks and as chronic if lasting more than 12 weeks.

3. FINDINGS

3.1. Total cervical disc replacement

For the clinical effectiveness and safety literature review, two recent systematic reviews, including a Cochrane review from 2012[3] and another review from 2014[4], were found and updated with five additional randomised controlled trials (RCTs).[5-9] Concerning the economic literature, the sole systematic review of economic evaluations of CTDR identified was discarded because of its poor results of our qualitative appraisal. Our analysis is instead based on five original cost-utility analyses published between 2013 and 2014, comparing CTDR to fusion (and to discectomy without fusion among the comparators in one study).[10-14] No trials or economic evaluations including conservative treatment as a comparator were found. Besides, experts argued that surgery is performed for the management of arm pain and that a prolonged conservative treatment would only be relevant in patients whose main complaint is neck pain. They also expressed strong doubts about the efficacy of discectomy without fusion, and further argued that such intervention was no standard practice in Belgium and therefore not a valid comparator.

3.1.1. Clinical effectiveness of CTDR versus fusion

The pooled analysis of data from RCTs favoured CTDR over fusion for single-level disease in the short (3 to 12 months), medium (2 years) and long term (4 years) for most outcomes:

- There is a significant functional difference in favour of CTDR measured by the Neck Disability Index (NDI).
- There is a significant difference in favour of CTDR in arm pain.
- There is a significant medium- and long-term difference in favour of CTDR in neck pain.
- Mobility at the operated level is significantly higher after CTDR than with fusion.
- Medium- and long-term quality of life is higher in the CTDR patient group.
- Patient satisfaction is high in both CTDR and fusion groups but is slightly higher in the CTDR group.

These results reached statistical significance. However, the thresholds predefined in agreement with the experts for a clinically important difference between the two techniques were not met for the main patient outcomes which are pain, quality of life and differences in functional status. In other words, none of the mean differences in these outcomes were clinically relevant.

The data on CTDR for multiple-level disease are scarce. As for single-level disease, results generally favoured CTDR over fusion, but there is a need for more trials to reliably determine clinical effectiveness in this patient group. Also, although often statistically significant, the results did not meet the thresholds for clinically important differences.

The Neck Disability Index

The Neck Disability Index (NDI) is a self-reported questionnaire used to determine the impact of neck pain on the patient's daily life. It consists of ten questions (Pain Intensity, Personal Care, Lifting, Reading, Headaches, Concentration, Work, Driving, Sleeping, and Recreation) scoring from 0 (no disability) to 5 (complete disability). All scores are totalled in a global score on a 0-50 scale (0 being the best possible score and 50 the worst) or on a 0-100 scale, often reported as a percentage.

3.1.2. Safety of CTDR versus fusion

The results on single-level disease outcomes related to safety in general also favoured CTDR over fusion although a non-significant difference between treatment groups were found more often than for clinical effectiveness:

- There is a significant medium-term difference in favour of CTDR for revision surgery at index level but not at adjacent levels.
- There is a significant long-term difference in favour of CTDR for the overall rate of revision surgeries at index and adjacent levels (combined).
- There is no significant difference in the rate of adjacent segment disease.

One of the main rationales for introducing CTDR, namely the prevention of adjacent segment disease, is therefore not yet confirmed. Additionally, our expert group noted that because this disease evolves slowly, an even longer follow-up (10 years) is needed before firm conclusions can be drawn. Secondly, with the introduction of CTDR there was a hope for a decreased rate of re-interventions. However, although the rate of re-interventions appears to be smaller in the group receiving CTDR, it was stressed by the experts that there are several limitations to the reporting of re-interventions in the literature. The Belgian experts argued that the complexity and the severity of a re-intervention after a CTDR are much greater than after a fusion. This argument, however, will require much larger study populations to be fully verified.

The safety data on CTDR for multiple-level disease are scarce. In the medium and long term, CTDR appears to have less subsequent surgical interventions and in the medium term also less device-related adverse events. However, there is a need for more trials to reliably determine safety in this patient group.

3.1.3. Cost-effectiveness of CTDR versus fusion

Despite the significant statistical (but not clinically relevant) difference in terms of quality of life favouring CTDR, the current literature review of economic evaluations highlighted that, compared to fusion, CTDR was not always the preferred option from a cost-effectiveness point of view. Depending on the economic evaluation, CTDR was either more cost-effective or less cost-effective than fusion.

The economic evaluations suffered from strong methodological flaws. Their horizon was limited to the time frame of the clinical studies they used (maximum 5 years) such that important long-term costs and consequences were ignored. For one study, the difference in terms of gain in quality of life between the interventions was supposed to remain the same over a 20-year period. This optimistic extrapolation assumption is however not supported by any RCT. No sensitivity analysis was performed to test this last assumption. Crucial input parameters such as quality of life, index- and adjacent-level reoperation rates and the adjacent segment degeneration, varied largely from one study to another. Furthermore, the results were prone to large variations when sensitivity analyses were performed. Relatively small variations on input parameters caused the initially favoured intervention to become less cost-effective than its alternative or vice-versa.

Finally none of the five economic evaluations was performed in Belgium, with costs and outcome data reflecting the Belgian health care system and organisation. Today, clinical evidence is lacking on crucial input parameters to be able to build a reliable Belgian model. Therefore, given the current lack of high-quality economic evaluations and awaiting better long-term information on crucial input parameters (quality of life, effect and rates of revision/reoperations and adjacent segment degeneration), it is difficult to draw definitive conclusions regarding the cost-effectiveness of CDTR versus fusion.

3.2. Total lumbar disc replacement

One 2012 Cochrane systematic review[15] was included, updated and complemented by companion papers that provided longer-term follow-up or additional outcomes from the already included RCTs.[16-19] Six RCTs compared LTDR with fusion and one RCT used conservative treatment (multidisciplinary rehabilitation approach including exercises and cognitive interventions) as a comparator. In agreement with the experts, studies mixing single- and multiple-level disease patients were withheld to keep as many study data as possible. Experts argued that the main origin of chronic low back pain is often difficult to determine, regularly also involving muscles or ligaments. Moreover, psychosocial factors might play an important role in this group of patients. Therefore, experts deemed cognitive behavioural intervention a valuable comparator for future research.

Concerning the economic evaluations, after qualitative appraisal no systematic literature review could be included in the present study. LTDR was compared to fusion in two[20-22] (see footnote b) out of the three original cost-utility analyses retrieved and to conservative treatment in the third one (based on the single RCT selected above).[23]

[b] Two articles were related to the same study.

3.2.1. Clinical effectiveness of LTDR versus fusion or conservative treatment

The RCTs generally suffer from limitations: no blinding, poor quality outcome reporting and a too short follow-up. The pooled analysis of RCT data in the short (6 months) and medium term (2 years) favoured LTDR over fusion for some outcomes but not for all. Additionally, although the majority of RCTs were initiated long ago, a number of them have not reported long-term follow-up results. The long-term clinical results **comparing LTDR to fusion** are therefore based only on 2 RCTs and should be interpreted with caution.

- There is a statistically significant back-specific functional difference measured by the Oswestry Disability Index (ODI) in the short and medium term in favour of LTDR. Two studies find that this difference is not maintained at 5 years.
- There is a statistically significant difference in the short and medium term in favour of LTDR for back pain measured by the VAS scale.
- No significant between group difference was found in the short and medium term for leg pain measured with the NRS scale.
- The short-, medium- and long-term results on quality of life varied amongst studies but were most often not statistically different between groups.
- Studies measuring mobility consistently found that mobility in the medium term in the LTDR group was comparable to preoperative status whereas mobility after fusion was nearly zero. However, the clinical implications of this are not clear.
- Patient satisfaction in the medium term is high in both the LTDR and the fusion group but is statistically significantly higher in the LTDR group.

It should be noted that the thresholds predefined in agreement with the experts for a clinically important difference between the two techniques were not met for the average main patient outcomes which are pain, patient satisfaction and differences in functional status. In other words, none of the mean differences in these outcomes were clinically relevant.

Only one RCT **comparing LTDR with conservative treatment** (rehabilitation) was identified. Results should therefore be interpreted with caution. This trial found statistically significant differences in favour of LTDR for most outcomes:

- There is a statistically significant back-specific functional difference measured by the ODI in favour of LTDR in the medium term.
- There is a statistically significant difference for back pain measured by the VAS scale in favour of LTDR in the medium term.
- In the medium term, there is a statistically significant difference in quality of life in favour of LTDR for the SF-36 physical component summary score but no significant difference for the SF-36 mental component summary score and the EQ-5D quality of life scale.
- No significant difference was found for mobility in the medium term.
- There is a statistically significant difference for patient satisfaction in favour of LTDR in the medium term.

The average improvement for back pain and functional status did not reach the thresholds for clinically important differences.

Outcome assessment instruments used in the included studies

The **Oswestry Disability Index (ODI)** is a tool measuring a patient's permanent low back functional disability. Each out of 10 questions consists of 6 possible answers translated into numerical values (0-6) with 0 being the best possible answer. These values are multiplied to percentage scores. A total score ranging 0-20% represents minimal disability, 21-40% moderate disability, 41-60% severe disability, 61-80% crippled and 81-100% bed-bound (or exaggerating the symptoms).

The pain **Visual Analog Scale (VAS)** is a widely used measure of pain intensity comprised of an axis, usually 100 mm long, anchored with two verbal descriptors: "no pain" (0 mm) and "pain as bad as it could be" or "worst imaginable pain" (100 mm). The score is measured with a ruler to the patient's mark.

The **Numeric Rating Scale (NRS)** for pain measures the pain intensity in adults. The most common version used is the 11-item NRS. The NRS is a segmented numeric version of the VAS in which a patient selects a whole integer (0–10) that best reflects his/her pain intensity, 10 indicating the greater pain intensity.

The **Generic Medical Outcomes Study Short Form 36 (SF-36)** is a self-reported questionnaire of 36 questions measuring the health related quality of life, covering 8 health dimensions (physical functioning, role limitations owing to physical health, bodily pain, general health perceptions, vitality, social functioning, role limitations owing to emotional health, and mental limitations in physical activities because of health problems). Each dimension is rated on a 0-100 score (0=maximum disability, 100=no disability). The four physical and mental domains are summarized, respectively in a SF-36 Physical Component summary Score (0-100) and SF-36 Mental Component summary Score (0-100).

The **Generic EuroQol 5 dimensions (EQ-5D)** is a self-reported questionnaire of 5 questions on health related quality of life, representing five health dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension is assessed on a 3-point scale: no problems, some problems, extreme problems. The combined EQ-5D is presented as a quasi-continuous outcome on a scale of 0-1.00 (death-'full health'). Sometimes negative numbers are used to represent health states valued as worse than death.

3.2.2. *Safety of LTDR versus fusion or conservative treatment*

There is insufficient evidence to determine safety outcomes for LTDR versus fusion as studies fail to examine important outcomes and do not report long-term results. From the few trials available it appears that:

- There is no statistically significant difference for the overall rate of reoperations.
- In the medium term there is no statistically significant difference for "adjacent segment problems". One trial finds a difference in favour of LTDR versus fusion for adjacent-level degenerative changes in the long term (5 years).

There is also insufficient evidence to determine safety outcomes for LTDR versus rehabilitation. From a single trial it appears that in the medium term there is no statistically significant difference in the rate of reoperations and in the rate of adjacent level degeneration.

3.2.3. *Cost-effectiveness of LTDR versus fusion or conservative treatment*

Results of the economic evaluations of LTDR versus fusion (2 studies) or conservative treatment (1 study) were diverse. Reflecting the results from the clinical assessment, no significant quality of life benefit could be associated with LTDR when compared to fusion. Whether LTDR was considered cost-effective, or not, depended on the study and the fusion technique chosen as comparator. Likewise, evidence on quality of life benefits for LTDR versus conservative treatment, which is also highly influential on the cost-effectiveness results, is too scant to draw any firm conclusion. Whatever the comparator, the duration and the extent of this effect over time remain unknown in the current literature.

The quality of the studies could be questioned; their time horizon was very short (2 years for all studies) thereby ignoring long-term effects. For two economic evaluations, the input parameters differed from those reported in the source RCTs without any explanation for the discrepancy.

Finally none of the three economic evaluations was performed in Belgium, with costs and outcome data reflecting the Belgian health care system and organisation. As for CTDR, given the current lack of high-quality economic evaluations and awaiting better long-term information on crucial input parameters (quality of life, effect and rates of revision/reoperations and adjacent segment degeneration), it is difficult to currently draw conclusions regarding the cost-effectiveness of LTDR versus fusion or versus conservative treatment.

RECOMMENDATIONS[c]

CERVICAL TOTAL DISC REPLACEMENT

To the Technical Medical Council and the Implants and Invasive Medical Devices Reimbursement Commission

- **From a clinical point of view, the cervical total disc replacement and the cervical fusion are roughly just as safe and effective in the short and medium term, while there is a lack of long-term data. Consequently, we recommend to keep the current reimbursement rules of the procedure, i.e. the reimbursement of the surgical procedure for cervical total disc replacement at the same tariff as the surgical procedure for cervical fusion, but under different nomenclature codes. There are currently not enough arguments yet to recommend a reimbursement of the cervical prosthesis without strict conditions.**

To the hospital responsibles and surgeons

- **In accordance with the law of 2002 relative to the patients' rights, the patient should be clearly informed of the respective advantages and disadvantages as well as the cost of each surgical alternatives.**

Recommendations for further clinical research

- **Larger-scale RCTs, including a long-term follow-up (at least 10 years) are needed to conclude on the risk of adjacent segment degeneration and to confirm the slightly lower revision rate compared to cervical fusion and the higher complexity of reintervention in case of cervical total disc replacement.**

LUMBAR TOTAL DISC REPLACEMENT

To the Technical Medical Council and the Implants and Invasive Medical Devices Reimbursement Commission

- **From a clinical point of view, the lumbar total disc replacement and the lumbar fusion are roughly just as safe and effective in the short and medium term, while there is a lack of long-term data. Consequently, we recommend to reimburse the surgical procedure for lumbar total disc replacement at the same tariff as the surgical procedure for lumbar fusion, but under different nomenclature codes. There are currently not enough arguments to recommend a reimbursement of the lumbar prosthesis without strict conditions.**

[c] The KCE has sole responsibility for the recommendations.

To the hospital responsibles and surgeons

- **In accordance with the law of 2002 relative to the patients' rights, the patient should be clearly informed of the respective advantages and disadvantages as well as the cost of each surgical alternatives.**

Recommendations for further clinical research

- **Current and future RCTs should extend their follow-up period (at least 10 years) to study the long-term effectiveness and safety of each procedures.**

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COLOPHON

Title:	Cervical and lumbar total disc replacements – Synthesis
Authors:	Kirsten Holdt Henningsen (KCE), Nancy Thiry (KCE), Chris De Laet (KCE), Sabine Stordeur (KCE), Cécile Camberlin (KCE)
Project coordinator and Senior supervisor:	Sabine Stordeur (KCE)
Reviewers:	Frank Hulstaert (KCE), Raf Mertens (KCE), Lorena San Miguel (KCE)
External experts:	Michael Bruneau (Belgian Society of Neurosurgery (BSN) – Hôpital Erasme, Bruxelles), Philippe Claesen (Jessa Ziekenhuis), Geert Crombez (UGent), Bart Depreitere (UZ Leuven), Hendrik Fransen (AZ St-Lucas Gent), Patrick Galloo (Socialistische Mutualiteiten), Alphonse Lubansu (Hôpital Erasme Bruxelles), Germain Milbouw (CHR Namur), Henri Nielens (Cliniques universitaires Saint-Luc, Bruxelles), Valérie Noblesse (INAMI – RIZIV), Bart Poffyn (UZ Gent), Stéphane Sobczak (AXXON), Johan Van Lerbeirghe (SSBE Spine Society of Belgium), Jan Van Meirhaeghe (AZ St-Jan Brugge), Patrick Van Schaeybroeck (Imelda Ziekenhuis, Bonheiden), Peter Van Wambeke (UZ Leuven), Dominique Verhulst (ZNA Stuivenberg, Antwerpen), René Westhovens (UZ Leuven)
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