KCE REPORT 189B

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

NEUROMODULATION POUR LA PRISE EN CHARGE DE LA DOULEUR CHRONIQUE : SYSTÈMES IMPLANTÉS DE NEUROSTIMULATION MÉDULLAIRE ET POMPES INTRATHÉCALES ANALGÉSIQUES

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KCE REPORT 189B
HEALTH TECHNOLOGY ASSESSMENT

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

NEUROMODULATION POUR LA PRISE EN CHARGE DE LA DOULEUR CHRONIQUE : SYSTEMES IMPLANTES DE NEUROSTIMULATION MEDULLAIRE ET POMPES INTRATHECALES ANALGESIQUES

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PRÉFACE

Ce n'est pas parce qu'un syndrome ne peut pas être bien mesuré ou objectivé, qu'on peut le juger sans importance. Il suffit de poser la question aux personnes souffrant de douleurs chroniques, qui les accablent du matin au soir, jour après jour, et souvent pendant des mois, voire des années. La douleur chronique a aussi un impact négatif sur leur vie sociale, et peut rendre leur vie professionnelle difficile, voire impossible à mener.

Beaucoup de personnes souffrant de douleurs chroniques ne voient jamais de spécialiste de la douleur, pratiquent l'automédication ou sont confrontées à des problèmes psychologiques ou d'addiction. Et même quand elles bénéficient d'un soutien professionnel adéquat, cela ne suffit pas toujours. Lorsque les antidouleurs, la kinésithérapie, le soutien psychologique ou d'autres traitements courants échouent, le patient – et souvent du même coup son médecin – se retrouve le dos au mur.

Prêt à tout essayer pour soulager ce calvaire incessant et insupportable, on fait alors appel aux médecines alternatives, mais aussi à des interventions invasives, coûteuses et comportant souvent des risques. Les deux techniques abordées dans ce rapport appartiennent à ces dernières solutions plus 'audacieuses'. Dans les deux cas, la technique aborde directement les voies nerveuses de la moelle épinière, soit par stimulation électrique, soit en injectant des antidouleurs dans le canal rachidien grâce à une pompe et un cathéter implantés.

Quelle est la place de ces techniques? A quel point sont-elles efficaces, et quels risques y sont liés? Enfin, leurs bénéfices compensent-ils les coûts et les risques encourus? Les grandes différences dans leur utilisation, que ce soit au niveau international ou au niveau belge, laissent déjà présager que les réponses ne sont pas évidentes. Nous espérons faire un peu la lumière à ce sujet grâce à ce rapport. Nous tenons à remercier les médecins de la douleur et les professionnels paramédicaux concernés qui nous ont fait bénéficier de leur expertise au cours de cette étude.

Raf MERTENS
Directeur Général

RÉSUMÉ

LA DOULEUR ET SA PRISE EN CHARGE

La prise en charge des douleurs chroniques sévères exige une approche multidisciplinaire incluant, en fonction de l'origine de la douleur, différentes spécialités médicales et paramédicales. La prise en charge des douleurs chroniques peut englober différents types d'intervention y compris l'administration d'antalgiques, des interventions chirurgicales et des thérapies physiques ou psychologiques mais également des procédures interventionnelles plus techniques. L'objectif de ce rapport est d'évaluer la contribution supplémentaire de la neuromodulation, à savoir les systèmes implantés de neurostimulation médullaire et les pompes intrathécales analgésiques, dans la prise en charge de la douleur.

La neurostimulation médullaire (SCS) utilisée dans la prise en charge de la douleur est une technique interventionnelle dont l'objectif est de court-circuiter une douleur réfractaire d'origine neuropathique en envoyant, à l'aide d'électrodes, des stimulations électriques sur la moelle épinière, provenant d'un générateur d'impulsions implanté.

Les pompes intrathécales analgésiques (IADP) disposent d'un réservoir médicamenteux implanté qui permet la libération continue d'analgésiques à travers un cathéter, à l'endroit voulu dans l'espace intrathécal.

Plusieurs pathologies douloureuses ont été suggérées comme des indications potentielles justifiant l'ajout de la neuromodulation à l'arsenal thérapeutique de lutte contre les douleurs chroniques. Les indications les plus fréquemment rencontrées dans la littérature sont : *le syndrome d'échec de la chirurgie du rachis* (*failed back surgery syndrome)*, *le syndrome douloureux régional complexe*, *l'ischémie critique des membres*, *l'angine de poitrine réfractaire* et *les douleurs cancéreuses réfractaires*.

EFFICACITÉ, SÉCURITÉ ET COÛT-EFFICACITÉ

Cette évaluation à été réalisée au moyen d'une recherche de la littérature pour laquelle la qualité des données probantes est faible, principalement a cause de raisons pratiques. Notre revue systématique des études randomisées contrôlées (RCT) a livré des données probantes de qualité faible à modérée de l'efficacité de la SCS chez les patients souffrant d'un syndrome d'échec de la chirurgie du rachis, d'un syndrome douloureux régional complexe, d'ischémie critique des membres et d'angine de poitrine réfractaire. En ce qui concerne l'efficacité des IADP, nous n'avons identifié que des données probantes de faible qualité dans le traitement des patients présentant des douleurs cancéreuses réfractaires. Aucune donnée probante d'efficacité n'a été trouvée pour les autres indications de la neuromodulation.

Un consortium académique de spécialistes de la douleur avait évalué précédemment les données probantes scientifiques pour plusieurs indications spécifiques y compris des données issues d'études observationnelles. Ce groupe est arrivé à des conclusions similaires aux nôtres et a formulé des recommandations positives pour la SCS dans le syndrome d'échec de la chirurgie du rachis, le syndrome douloureux régional complexe et l'angine de poitrine réfractaire, et pour IADP dans les douleurs cancéreuses réfractaires.

Dans l'ensemble, les effets indésirables graves sont assez rares. Des incidents directement liés à la chirurgie (infections, hémorragies) ou au fonctionnement du système ont été rapportés de temps en temps. Les problèmes de fonctionnement des IADP peuvent mener à un surdosage aigu ou à des symptômes de sevrage sévères menaçant le pronostic vital. Des problèmes de sécurité ont été également évoqués dans les études observationnelles, notamment liées à la délivrance intrathécale d'opioïdes, allant des complications endocriniennes générales à une augmentation du taux de mortalité, en passant par le développement de granulomes à l'extrémité du cathéter dans l'espace intrathécal.

La neuromodulation (SCS et IADP) ne peut être envisagée que chez certains patients soigneusement sélectionnés après une évaluation approfondie par une équipe véritablement multidisciplinaire composée de spécialistes de la douleur, dans un centre expérimenté, spécialisé dans le traitement de la douleur.

En raison du manque de données relatives à l'efficacité, la qualité des données portant sur le rapport coût-efficacité est également pauvre.

RÉGLEMENTATIONS ET REMBOURSEMENT

Les règles de remboursement belges actuelles pour l'utilisation et le remboursement de la SCS et des IADP diffèrent singulièrement de celles de nos pays voisins, à savoir la France, l'Allemagne, le Royaume-Uni et les Pays-Bas.

De manière générale, les indications de la neuromodulation en Belgique sont limitées uniquement aux douleurs neuropathiques. Cependant, le syndrome douloureux régional complexe a été spécifiquement exclu des indications en Belgique. De plus, toujours en Belgique, les indications sont presque les mêmes pour la SCS comme pour les IADP.

Aucun des quatre autres pays ne propose par ailleurs une réglementation tout à fait claire et on note des incohérences au niveau des indications acceptées. Ce manque de clarté est probablement lié à la difficulté de définir clairement les mécanismes de la douleur et à l'absence de données d'efficacité convaincantes.

Comme mentionné précédemment les indications acceptées pour les IADP sont presque les mêmes en Belgique que pour la SCS tandis que dans d'autres pays, les règles d'utilisation des deux techniques diffèrent. Ainsi en Belgique, contrairement à ce qui se fait dans d'autres pays, la douleur cancéreuse réfractaire n'est pas explicitement mentionnée comme une indication de l'IADP alors qu'en pratique elle représente une indication acceptée pour le remboursement.

La durée de la période d'essai constitue une autre différence importante: elle est de quatre semaines en Belgique mais beaucoup plus courte dans les autres pays.

UTILISATION ET COÛTS

En Belgique, le nombre annuel d'implants de SCS (primo-implantations et remplacements) a augmenté et est passé de moins de 700 en 2002 à environ 900 en 2009. Le nombre des implants IADP est resté relativement stable, avec moins de 200 implants par an. Les dépenses INAMI annuelles totales directement liées aux implants de neuromodulation ont été estimées à près de € 12,5 millions pour l'année 2009.

L'utilisation de la neurostimulation varie largement d'un hôpital à l'autre ainsi que d'une région à l'autre. Cinquante-cinq hôpitaux ont placé des implants de neuromodulation entre 2002 et 2008 mais le nombre d'implants varie fort par hôpital et un seul hôpital a implanté plus d'un quart du nombre total. La majorité des implants ont été posés en Flandre.

Les chiffres belges de l'utilisation de la neuromodulation sont nettement plus élevés que ceux notés dans les quatre autres pays. En Belgique on implante, par an, 85 systèmes de SCS et 18 IADP par million d'habitants. Ces chiffres sont nettement plus bas dans les autres pays.

Nos données ont montré qu'environ 60% des patients chez qui on place un implant de neuromodulation sont des femmes et que l'âge moyen est de 52 ans pour les SCS et de 55 ans pour les IADP.

Selon les experts de terrain, la principale indication pour l'usage de SCS en Belgique est le syndrome d'échec de la chirurgie du rachis. Nos données ne nous ont permis ni de le valider ni de l'invalider parce que les données diagnostiques des hôpitaux s'avèrent trop peu spécifiques dans le cas de cette technique. Toujours est-il que dans le passé, l'incidence de la chirurgie rachidienne s'est révélée être plus élevée en Belgique que dans les pays voisins, ce qui pourrait mener à un nombre relativement plus élevé d'échecs de cette chirurgie. Il est certes plausible que ce nombre élevé d'échecs soit à son tour lié au taux élevé d'utilisation de la neuromodulation en Belgique mais les données ne permettent pas de le confirmer. Des indices indirects, comme la fréquence plus élevée des chirurgies rachidiennes en Belgique et une distribution régionale de l'incidence des chirurgies rachidiennes similaire à la distribution du recours à la neuromodulation, peuvent fournir quelques clés pour comprendre ce problème mais des données détaillées sur les patients manquent afin d'éclaircir totalement cette question.

CONCLUSION

Les données probantes disponibles ne fournissent que des preuves limitées d'efficacité et de coût-efficacité de la neuromodulation. Les indications les mieux documentées pour la SCS sont le syndrome d'échec de la chirurgie du rachis, le syndrome douloureux régional complexe, l'ischémie critique des membres et l'angine de poitrine réfractaire. Pour les IADP, l'indication la mieux documentée est celle des douleurs cancéreuses réfractaires.

La neuromodulation (SCS et IADP) est une technique interventionnelle qui doit être considérée comme la dernière étape possible de l'approche multi-niveaux de la prise en charge des douleurs chroniques réfractaires. Elle ne peut clairement constituer qu'un élément limité au sein d'un plus large éventail d'interventions dans le cadre d'une approche multidisciplinaire de cette prise en charge. En raison du manque de données probantes disponibles, la neuromodulation ne peut être envisagée qu'en dernier recours chez les patients pour lesquels le reste de l'arsenal thérapeutique n'a pas permis d'arriver à un soulagement satisfaisant de la douleur. L'évaluation complète dans un centre multidisciplinaire de la douleur en constitue une condition supplémentaire préalable. Les équipes multidisciplinaires doivent aussi, selon l'origine de la douleur, faire appel à d'autres spécialistes, par exemple à des chirurgiens vasculaires, des cardiologues, des oncologues ainsi qu'aux professionnels paramédicaux spécialisés.

Les règles belges actuelles en matière de remboursement sont en pratique plutôt vagues, en grande partie parce que le terme *'douleur neuropathique' ouvre la voie à l'interprétation*. De plus, les indications approuvées manquent souvent de cohérence avec les données probantes, ce qui est également le cas à l'étranger. Ces incohérences apparaissent clairement quand on compare les indications approuvées entre les différents pays.

Comme on pouvait s'y attendre, l'utilisation de la SCS et des IADP montre une grande variabilité entre les pays en termes de nombre de dispositifs implantés. Le volume de la neuromodulation est plus élevé en Belgique que dans les pays voisins. La Belgique fait par ailleurs preuve d'une grande variabilité géographique nationale et certains de ses centres sont de réels outliers. Même sans tirer de conclusion sur un quelconque lien de causalité, cette distribution géographique relativement inégale pose question par rapport à l'adéquation des interventions et à l'équité en termes d'accès au traitement.

Etant donné le faible niveau de preuve, il est important que les patients soient informés des incertitudes concernant l'efficacité et la sécurité de ces techniques, la durée de vie limitée des piles des dispositifs et, par conséquent, de la probabilité élevée d'une ré-intervention.

RECOMMANDATIONS[a]

A l'attention du Ministre, après avis des organes compétents :

- **Les indications pour la neuromodulation admissibles pour un remboursement devraient être revues :**
  - **Elles devraient mieux correspondre à l'évidence (limitée) disponible en la matière.**
  - **La neuromodulation ne devrait être considérée comme une des dernières étapes thérapeutiques qu'après que les méthodes moins invasives ont été épuisées dans une approche par étapes, intégrée et multidisciplinaire.**
  - **L'adaptation de la réglementation devrait se faire en concertation étroite avec les sociétés scientifiques des anesthésistes spécialisés dans le traitement de la douleur chronique et avec l'apport des paramédicaux et d'autres spécialistes (neurochirurgiens, orthopédistes, chirurgiens vasculaires, cardiologues, oncologues …) en fonction de l'indication spécifique.**
- **Pour le syndrome d'échec de la chirurgie du rachis *(failed back surgery syndrome)*, il existe des raisons de croire que l'indication même pour la chirurgie dorsale devrait être réexaminée de façon critique.**
- **Une réduction de la durée de la période d'essai entre l'implantation de l'électrode / du cathéter et du stimulateur / de la pompe pourrait être envisagée. Il est également recommandé de rassembler, dans un cadre restreint et sous des conditions strictes, des données sur l'efficacité, la sécurité et les modalités de la période d'essai pour étayer les décisions futures.**
- **Les données nécessaires manquent actuellement pour évaluer la place précise des stimulateurs rechargeables dans le système de remboursement. Les prix très élevés de ces appareils rechargeables devraient être examinés de manière critique.**
- **Actuellement, la prise en charge multidisciplinaire de la douleur chronique est surtout organisée sur base de projets pilotes temporaires. Une approche plus structurée, couplée à des mesures de résultats, est dès lors souhaitable.**

[a] Le KCE reste seul responsable des recommandations faites aux autorités publiques

- **La capacité et la répartition géographique nécessaires des centres du traitement de la douleur, leur niveau de service attendu et les exigences professionnelles quant aux collaborateurs doivent être définis de manière plus détaillée. Les données nécessaires pour cette définition sont disponibles.**

Recommandations pour les professionnels de la santé :

- **Les sociétés scientifiques compétentes devraient être encouragées à développer des recommandations de bonne pratique clinique pour les patients souffrant de douleur chronique réfractaire.**
- **Les cliniciens et les soignants doivent suffisamment informer les patients à propos de la neuromodulation et plus spécifiquement en ce qui concerne le manque de données probantes relatives à l'efficacité et la sécurité et en ce qui concerne la durée limitée des piles, ce qui induit un risque de ré-intervention.**

Recommandations pour de futures recherches :

- **Il existe un manque important de données probantes relatives à l'efficacité et à la sécurité de la neuromodulation, et pour lesquelles une recherche interventionnelle de bonne qualité est nécessaire. Cette recherche devrait de préférence être organisée de manière multicentrique et au niveau international.**
- **Une meilleure prévision de la durée de vie des piles est souhaitable et devrait être possible sur base des paramètres d'installation de l'appareil. Il s'agit d'une tâche importante pour l'industrie qui développe ces appareils.**

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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
AP	Angina Pectoris
APR-DRG	All Patient Refined Diagnosis Related Group
CABG	Coronary Artery Bypass Graft
CLI	Critical Limb Ischemia
CRPS	Complex Regional Pain Syndrome
EQ-5D	EuroQoL 5 dimensions
FBSS	Failed Back Surgery Syndrome
FOD–SPF	Refers to the Belgian Ministry of Health (Federale Overheidsdienst Volksgezondheid, Veiligheid van de Voedselketen en Leefmilieu – Service Public Fédéral santé publique, sécurité de la chaîne alimentaire et environnement, Belgium)
HADS	Hospital Anxiety and Depression Score
HRQoL	Health Related Quality of Life
HTA	Health Technology Assessment
IADP	Intrathecal Analgesic Delivery Pump (= IDDS)
IASP	International Association for the Study of Pain
ICER	Incremental Cost Effectiveness Ratio
IDD	Intrathecal Drug Delivery
IDDS	Intrathecal Drug Delivery System (= IADP)
INAHTA	International Network of Agencies for Health Technology Assessment
INAMI–RIZIV	Institut National d'Assurance Maladie et Invalidité (NIHDI, Belgium)
INS	International Neuromodulation Society
IPG	Implantable Pulse Generator
MeSH	Medical Subject Heading
MPC	MultiAlldisciplinary Pain Centre
NICE	National Institute for Clinical Excellence (UK)
NIHDI	National Institute for Health and Disability Insurance (=RIZIV – INAMI, Belgium)
NPRS	Numeric Pain Rating Scale (=NRS)
NRS	Numeric Rating Scale (=NPRS)
NVAsP	Nederlandse Vereniging voor Anesthesiologie, Sectie Pijnbestrijding

OA – VI	Organismes Assureurs – Verzekeringsinstellingen
PGIC	Patients' Global Impression of Change scale
PMR	Percutaneous Myocardial laser Revascularisation
PVD	Peripheral Vascular Disease
QALY	Quality Adjusted Life Year
QoL	Quality of Life
RAP	Refractory Angina Pectoris
RDQ	Roland Disability Questionnaire
RCT	Randomised Controlled Trial
RD	Royal Decree (Koninklijk Besluit (KB) – Arreté Royal (AR), (Belgium)
RIZIV – INAMI	RijksInstituut voor Ziekte en Invaliditeits Verzekering – Institut national d'assurance maladie-invalidité (NIHDI, Belgium)
SAQ	Seattle Angina Questionnaire
SCS	Spinal Cord Stimulation
SF-36	Medical Outcome Study Short Form 36-Item Health Survey
TENS	Transcutaneous Electrical Nerve Stimulation
VAS	Visual Analogue Scale

SYNTHÈSE

1. OBJECTIF ET PORTÉE

La prise en charge des douleurs chroniques sévères exige une approche multidisciplinaire incluant, en fonction de l'origine de la douleur, différentes spécialités médicales et paramédicales. La prise en charge des douleurs chroniques peut englober différents types d'intervention y compris l'administration d'antalgiques, des interventions chirurgicales et des thérapies physiques ou psychologiques mais également des procédures interventionnelles plus techniques.

L'objectif de ce rapport est d'évaluer la contribution supplémentaire de la neuromodulation, à savoir les systèmes implantés de neurostimulation médullaire et les pompes intrathécales analgésiques, dans la prise en charge de la douleur.

Dans le cadre de ce rapport, la neuromodulation a été limitée à (1) la neurostimulation médullaire (SCS – Spinal Cord Stimulation) à l'aide d'un stimulateur implantable et (2) les pompes implantables intrathécales analgésiques (IADP – Intrathecal Analgesic Delivery Pump). D'autres techniques, telles que la stimulation cérébrale profonde du cortex moteur et des nerfs périphériques n'ont pas été incluses dans ce rapport. L'utilisation de pompes intrathécales avec des médicaments non-analgésiques pour des indications autres que la douleur, plus spécifiquement le baclofène pour le traitement de la spasticité, ne font pas l'objet de ce rapport.

L'objectif de ce rapport est plus précisément:

1. D'évaluer les données probantes disponibles dans les études interventionnelles sur l'efficacité, la sécurité et le rapport coût-efficacité.
2. De décrire l'utilisation actuelle de ces techniques en Belgique et de la comparer à celle dans les pays voisins.
3. De formuler des recommandations en vue de l'intégration optimale des techniques de neuromodulation dans la prise en charge des douleurs chroniques.

Les informations ont été rassemblées par le biais de la combinaison d'une revue systématique de la littérature revue par des pairs, de la littérature grise et d'une analyse des données belges sur l'utilisation de ces techniques en 2002-2009.

2. LES DOULEURS CHRONIQUES ET LEUR PRISE EN CHARGE

2.1. Comment définir et mesurer la douleur?

La douleur, et plus spécifiquement les douleurs chroniques, sont un phénomène complexe. La douleur est, par définition, intrinsèquement subjective et impossible à mesurer avec précision. Cette caractéristique fait l'objet d'un vif débat sur la manière de définir et de classifier les différentes formes de douleur. Bien qu'il soit difficile d'évaluer précisément la douleur, elle a indéniablement un impact majeur sur la santé, sur la qualité de vie liée à la santé et sur notre fonctionnement.

Pour des raisons de cohérence, nous avons essayé de nous en tenir aux définitions générales utilisées par l'International Association for the Study of Pain (IASP) qui définit la douleur comme *'une expérience sensorielle et émotionnelle désagréable, associée à un dommage tissulaire réel ou potentiel, ou décrite en termes d'un tel dommage*. Cette définition est vaste mais vague et plusieurs définitions spécifiques y ont été ajoutées pour affiner la classification des différents aspects de la douleur.

Pour les études cliniques, les instruments génériques les plus utilisés sont l'échelle visuelle analogue (VAS – Visual Analogue Scale) qui demande que le patient indique le niveau de douleur sur une ligne continue de 100 mm, et sa variante numérique, l'échelle numérique pour l'évaluation de la douleur (NPRS – Numeric Pain Rating Scale).

2.2. Douleur nociceptive versus douleur neuropathique

Les principales distinctions entre les différentes causes de la douleur reposent sur les concepts de douleur nociceptive et de douleur neuropathique. La douleur nociceptive est la forme la plus courante de douleur *« normale »* aiguë. Dans ce type de douleur, une lésion tissulaire provoque une douleur. Le plus souvent, ce type de douleur est transitoire sauf, bien sûr, si la lésion tissulaire persiste.

Dans la douleur neuropathique, les choses sont différentes étant donné que la douleur est sont due à une lésion ou à une maladie du système nerveux somatosensoriel. Cette lésion ou cette maladie peuvent être dues à une anomalie structurale, à un traumatisme accidentel ou électif comme une chirurgie ou encore à une pathologie sous-jacente.

2.3. Douleur chronique

La durée minimum nécessaire pour qualifier une douleur de chronique est arbitraire mais il est généralement admis qu'elle doit être de 6 mois à un an. Passé ce délai, la douleur devient une pathologie à part entière et n'est plus considérée comme la simple manifestation d'un problème physique sous-jacent.

Etant donné le caractère vague de ces définitions générales, l'épidémiologie de la douleur chronique dans la littérature est très incertaine et principalement dépendante de définitions ad-hoc. Dans la pratique, les enquêtes par entretien sur la santé, les enquêtes de santé par examen et les études démographiques utilisent des définitions différentes et incompatibles dans le cadre de l'évaluation de la douleur chronique.

Par exemple, dans la dernière enquête par entretien sur la santé (2008) réalisée en Belgique, 12% des répondants ont rapporté avoir souffert de douleurs sévères au cours des quatre dernières semaines ; une prévalence par ailleurs en hausse avec l'âge. Mais la définition de ces douleurs sévères ne correspond toutefois pas à la définition des douleurs chroniques mentionnées plus haut. Un rapport récent du SPF Santé publique ainsi que d'autres sources estiment qu'environ 8,5% de la population, soit environ 1 million de Belges, pourraient avoir besoin d'une forme de traitement spécialisé de la douleur en raison de douleurs chroniques. Il convient toutefois de faire remarquer que seul un petit nombre de ces Belges entrerait en ligne de compte pour recevoir un traitement par neuromodulation.

2.4. Prise en charge des douleurs chroniques

La prise en charge des douleurs chroniques est elle aussi complexe ; au point même d'être devenue une discipline médicale à part entière. L'IASP préconise une prise en charge multidisciplinaire de la douleur chronique et la participation à cette prise en charge de différentes disciplines cliniques et autres disciplines des soins de santé : médecins, infirmières, professionnels de la santé mentale, physiothérapeutes, etc. Le choix de ces disciplines dépend aussi de la cause pathologique des douleurs chroniques.

Il n'existe pas de *'gold standard'* diagnostique ou therapeutique et très souvent les approches thérapeutiques antérieures ont échoué. La prise en charge des douleurs chroniques nécessite avant tout et surtout une approche par étape. Plusieurs options thérapeutiques sont disponibles et elles doivent être choisies en fonction de leur bénéfice potentiel optimal pour le patient. Outre évaluer et traiter la cause sous-jacente, l'approche symptomatique multidisciplinaire peut aussi comprendre le recours à des analgésiques, à une aide psychologique ou à une physiothérapie. L'étape suivante est une approche à plusieurs niveaux et peut envisager plusieurs traitements plus interventionnels, notamment des analgésies périphériques, des infiltrations de stéroïdes, un traitement par radiofréquence ou d'autres traitements encore.

La neuromodulation, y compris la neurostimulation et les pompes à analgésiques intrathécales, se situe en toute fin de la chaîne de cette approche à plusieurs niveaux. Ces techniques constituent le sujet de ce rapport.

3. TECHNIQUES DE NEUROMODULATION

La neurostimulation médullaire (SCS) utilisée dans la prise en charge de la douleur est une technique interventionnelle dont l'objectif est de court-circuiter une zone de douleur réfractaire d'origine neuropathique en envoyant, à l'aide d'électrodes positionnées en dehors de la dure mère (épidurale), des stimulations électriques sur la moelle épinière. Ces électrodes sont connectées à un générateur d'impulsions implanté dans une autre région du corps.

Les pompes intrathécales analgésiques (IADP) disposent d'un réservoir médicamenteux implanté qui permet la libération continue d'analgésiques à travers un cathéter positionné à l'intérieur de l'espace intrathécale de la colonne vertébrale. Leur principal objectif est de délivrer l'analgésique beaucoup plus près des récepteurs du système nerveux central au niveau choisi. Les IADP sont soit une pompe à débit continu (avec la possibilité supplémentaire de faire des injections en bolus) soit une pompe programmable à débit variable. Actuellement, la préférence semble aller à la pompe programmable qui est le type de pompe le plus souvent utilisé.

L'implantation d'un tel système se fait en deux étapes. Après avoir implanté les électrodes ou les cathéters, ces derniers sont connectés à un stimulateur externe ou à une pompe à médicament externe pour une période d'essai. Lorsque l'essai est concluant, une implantation permanente a lieu. En Belgique, cette période d'essai doit être d'au moins quatre semaines, mais dans d'autres pays elle est beaucoup plus courte et peut aller de cinq jours à deux semaines ou parfois même pas d'essai du tout.

Pour les deux dispositifs, le spécialiste médical peut toujours modifier les réglages après l'implantation et le patient peut aussi agir de manière limitée sur ces réglages à l'aide d'un dispositif de commande à distance.

Aussi bien la SCS que les IADP programmables fonctionnent à l'aide de piles. Lorsque les piles sont plates, généralement après quelques années de fonctionnement, le dispositif arrête de fonctionner. Dans ce cas, et aussi longtemps que le patient tire un bénéfice suffisant de ce type de traitement, le dispositif est remplacé dans le cadre d'une nouvelle intervention chirurgicale. La durée de vie des derniers dispositifs de SCS aurait été allongée et serait de 4 à 8 ans. Depuis peu, on trouve aussi des systèmes rechargeables en transcutané mais ces appareils son beaucoup plus chères. De manière générale, les piles des systèmes IADP qui consomment moins d'énergie ont une plus longue durée de vie que celles des systèmes de SCS non rechargeables.

4. LES INDICATIONS LES PLUS FRÉQUENTES

Plusieurs pathologies douloureuses ont été suggérées comme des indications justifiant potentiellement l'ajout de la neuromodulation à l'arsenal thérapeutique de lutte contre les douleurs chroniques. Ces indications sont considérées comme purement neuropathiques, ou comme un mélange de douleur neuropathique et nociceptive. Les indications les plus fréquemment rencontrées dans la littérature sont *le syndrome d'échec de la chirurgie du rachis (failed back surgery syndrome)*, *le syndrome douloureux régional complexe*, *l'ischémie critique des membres*, *l'angine de poitrine réfractaire* et *les douleurs cancéreuses réfractaires*.

Syndrome d'échec de la chirurgie du rachis

Le syndrome d'échec de la chirurgie du rachis se présente sous la forme de douleurs dans le dos pouvant ou non inclure des douleurs irradiant vers la jambe qui persistent après une ou plusieurs interventions chirurgicales rachidiennes. Il s'agit d'un mélange de douleurs neuropathiques et nociceptives, du dos et des jambes, qui n'ont pas répondu à *ce qu'on appelle* un traitement chirurgical *'anatomiquement réussi'*.

Syndrome douloureux régional complexe

Le syndrome douloureux régional complexe est un syndrome douloureux neuropathique composé d'une douleur régionale accompagnée d'œdème/d'altérations vasomotrices/sudorales observé après un évènement nocif ou une lésion nerveuse dans le cadre de complications post-chirurgicales ou d'un traumatisme. Il siège le plus souvent à une extrémité et peut aussi apparaître spontanément. La fracture est l'événement déclencheur le plus fréquent quand il se situe au niveau des extrémités supérieures. Ce syndrome a été décrit pour la première fois par Südeck il y a plus d'un siècle.

Ischémie critique des membres

La douleur ischémique apparaît lorsqu'un organe n'est plus suffisamment irrigué pour assurer ses besoins métaboliques. L'ischémie critique des membres est la manifestation de la douleur ischémique de l'artériopathie périphérique et se caractérise par des douleurs ischémiques chroniques au repos ou des lésions cutanées ischémiques. Elle se rencontre surtout chez des patients de plus de 55 ans et est souvent due à la progression d'une artériopathie.

Angine de poitrine réfractaire

L'angine de poitrine est une douleur ischémique thoracique sévère, généralement due à une coronaropathie. Le terme d'angine de poitrine réfractaire est utilisé quand les crises d'angine de poitrine ne peuvent pas être contrôlées à l'aide d'un traitement médicamenteux optimal et/ou une intervention chirurgicale comme un pontage aorto-coronarien ou des interventions coronariennes percutanées.

Douleurs cancéreuses réfractaires

Le traitement de la douleur chez les patients cancéreux dépend de la nature des douleurs, généralement un mélange entre des douleurs nociceptives et neuropathiques. La technique de la neuromodulation la plus fréquemment liée à cette indication dans la littérature est l'IADP pour le traitement des douleurs réfractaires à l'aide d'analgésiques systémiques.

5. EFFICACITÉ ET SECURITÉ

L'efficacité et la sécurité n'ont été étudiées que dans un petit nombre d'études cliniques randomisées et contrôlées (RCT – Randomised Clinical Trial). La qualité des données probantes issues de ces études est limitée en raison de plusieurs barrières auxquelles se heurte la recherche interventionnelle sur cette technologie. La principale barrière à ce niveau réside dans la quasi impossibilité de mettre en place des conditions en double aveugle pour les patients et le personnel médical. En cas de mise en place d'un traitement simulé, p. ex. d'un système de SCS, le patient remarque systématiquement la présence ou l'absence de stimulation. Une autre barrière importante à une recherche interventionnelle de qualité réside dans la difficulté de définir des critères d'évaluation et de les mesurer ensuite étant donné qu'on ne dispose pas de mesures quantitatives objectives de la douleur.

Les données probantes fournies par la recherche interventionnelle sont donc limitées et/ou de faible qualité. Les principales raisons de cette situation, outre les problèmes de randomisation et de double aveugle résident également dans les tailles d'échantillon relativement limitées et les délais de suivi relativement courts principalement attribuables à l'important cross-over entre les groupes de contrôles et les groupes de traitement.

5.1. Preuve d'efficacité limitée

Notre revue systématique des RCT a montré une qualité de preuve faible à modérée de l'efficacité de la SCS chez les patients souffrant d'un syndrome d'échec de la chirurgie du rachis, d'un syndrome douloureux régional complexe, d'ischémie critique des membres et d'angine de poitrine réfractaire. En ce qui concerne l'efficacité des IADP dans le traitement des patients présentant des douleurs cancéreuses réfractaires, on n'a trouvé que des données probantes de faible qualité et aucune preuve d'efficacité n'a été trouvée pour les autres indications de la neuromodulation.

Un consortium académique de spécialistes de la douleur a évalué précédemment les données probantes de plusieurs indications spécifiques séparément, y compris des données probantes issues d'études observationnelles. Utilisant une approche de gradation formelle de

l'évidence il sont arrivés à des conclusions similaires sur la base desquelles ils ont émis des recommandations positives pour la SCS dans le syndrome d'échec de la chirurgie du rachis, le syndrome douloureux régional complexe et l'angine de poitrine réfractaire et pour les IADP dans les douleurs cancéreuses chroniques. Ils ont également souligné que ces techniques de neuromodulation ne doivent être utilisées que dans des centres hautement spécialisés dans le traitement de la douleur.

5.2. Sécurité

Les RCT ne conviennent pas idéalement à la documentation des effets indésirables mais certains effets indésirables ont néanmoins été rapportés. D'autres l'ont aussi été dans des études observationnelles.

Les effets indésirables graves sont assez rares. Des incidents directement liés à la chirurgie (infections, hémorragie) ou au fonctionnement du système on été rapportés de temps en temps. Les problèmes de fonctionnement des IADP peuvent mener à un surdosage aigu ou à des symptômes de sevrage sévères et peuvent donc menacer le pronostic vital.

Des problèmes de sécurité ont été également évoqués dans les études observationnelles, notamment liées à la délivrance intrathécale d'opioïdes, allant des complications endocriniennes générales à une augmentation du taux de mortalité, en passant par le développement de granulomes à l'extrémité du cathéter dans l'espace intrathécale.

5.3. Conclusion

La neuromodulation (SCS et IADP) ne peut être envisagée que chez certains patients soigneusement sélectionnés après une évaluation approfondie par une équipe véritablement multidisciplinaire composée de spécialistes de la douleur, dans un centre expérimenté, spécialisé dans le traitement de la douleur. Son application à un patient spécifique doit être précédée d'une prise en charge sérieuse par étape de la douleur lorsque les options thérapeutiques moins invasives ont échoué. Il s'agit d'une approche interventionnelle qui n'est pas sans risque et les données probantes de son efficacité sont limitées.

6. EVALUATION ECONOMIQUE

Le manque de données probantes d'efficacité de qualité a des répercussions directes sur l'évaluation du rapport coût/efficacité. Alors que les prix et les coûts des interventions sont généralement bien connus, il persiste de nombreuses incertitudes sur l'impact de la SCS et des IADP sur les résultats cliniques tangibles, la qualité de vie et les coûts supplémentaires ou évités tels que ceux des médicaments adjuvants, etc.

Nous n'avons identifié que quelques études sur le rapport coût-efficacité fondées sur des RCT et ces études présentaient les mêmes faiblesses que celles identifiées pendant notre revue des données probantes cliniques: échantillons de petite taille, horizons de temps limités et absence de double aveugle. Les autres évaluations économiques modélisées reposaient sur de multiples hypothèses, rarement bien étayées par des données probantes. Un important point d'incertitude persiste au niveau de la durée de vie des piles des dispositifs et l'impact de cette caractéristique sur les coûts globaux de l'intervention.

Malgré les données probantes disponibles sur le syndrome d'échec de la chirurgie du rachis et le syndrome douloureux régional complexe, dans l'ensemble, il semble que la SCS pourrait s'avérer rentable aux valeurs seuils fréquemment rapportées (voir tableau 7 dans le rapport scientifique), mais la faible qualité des données probantes ne permet pas de tirer des conclusions claires à ce niveau. Chez les patients souffrant d'angine de poitrine réfractaire, les données probantes disponibles sur le rapport coût-efficacité n'ont pas été concluantes et pour les patients souffrant d'ischémie critique chronique, on ne dispose d'aucune donnée sur ce rapport.

Les résultats globaux sur le rapport coût-efficacité de la SCS ont été particulièrement influencés par les hypothèses sur les coûts et l'efficacité du dispositif, la durée de vie des piles du générateur d'impulsions, les coûts globaux des traitements antidouleur adjuvants et le coût des *'soins courants'.*

Chez les patients souffrant d'un syndrome d'échec de la chirurgie du rachis les rares données probantes disponibles sur le rapport coût-efficacité des IADP ne suffisent pas pour tirer la moindre conclusion définitive, et ceci plus spécialement en raison du manque de données probantes sur leur efficacité.

7. REGLEMENTATIONS ET REMBOURSEMENT

Les règles actuelles de remboursement de la SCS et des IADP en Belgique diffèrent largement de celles en vigueur dans quatre de nos pays voisins, à savoir la France, l'Allemagne, le Royaume-Uni et les Pays-Bas.

Toutefois, dans les cinq pays, la prise en charge des douleurs chroniques doit être effectuée par une équipe multidisciplinaire spécialisée dans la prise en charge des douleurs.

7.1. Indications

La réglementation belge spécifique est complexe et détaillée, mais pas toujours transparente. De manière générale, la règle est que les indications de la neuromodulation sont limitées uniquement aux douleurs neuropathiques. Toutefois, la définition et le diagnostic de la douleur ou sa nature neuropathique peuvent être sujets à interprétation. Pour éviter certains problèmes d'interprétation, le syndrome douloureux régional complexe a été spécifiquement exclu des indications en Belgique. De plus, toujours en Belgique, les indications éligibles à la SCS et aux IADP sont pratiquement les mêmes.

Aucun des quatre autres pays ne propose par ailleurs une réglementation tout à fait claire et on note des incohérences au niveau des indications acceptées. Ce manque de clarté est probablement lié à la difficulté de définir clairement les mécanismes de la douleur et à l'absence de données d'efficacité convaincantes.

Pour la SCS, il n'a pas été clairement établi pourquoi certaines indications telles que le syndrome d'échec de la chirurgie du rachis ou la pancréatite chronique sont acceptées en Belgique alors que malgré des données probantes comparables, le syndrome douloureux régional complexe en est explicitement exclu. Dans certains des quatre autres pays, des indications telles que le syndrome douloureux régional complexe ou l'angine de poitrine réfractaire constituent des indications acceptées, tandis que la pancréatite chronique ne l'est pas ou pas explicitement du moins. Ces différences semblent refléter les incertitudes actuelles sur les réelles indications de la neuromodulation.

Comme mentionné précédemment les indications acceptées pour les IADP, en Belgique sont pratiquement les mêmes que celles pour la SCS tandis que dans d'autres pays, les règles de remboursement des deux techniques sont différentes. De ce fait, et contrairement à ce qui est le cas dans d'autres pays, en Belgique, la douleur cancéreuse réfractaire n'est pas explicitement mentionné comme une indication de l'IADP alors qu'en pratique, elle est acceptée pour le remboursement. On dispose cependant de peu de données probantes scientifiques étayant l'efficacité des IADP dans la prise en charge des douleurs non cancéreuses.

7.2. Durée de la période d'essai

Une autre différence importante est celle notée au niveau de la durée de la période d'essai : elle est de quatre semaines en Belgique et beaucoup plus courte (cinq jours à deux semaines selon le pays) dans les autres pays. De plus, cette plus longue période d'essai en Belgique ne débouche pas sur beaucoup de conclusions négatives à l'issue de la période de test. Plus de 90% des essais ont un résultat positif et sont suivis d'une implantation.

7.3. Choix de l'implant

En Belgique, la règle spécifique à l'utilisation des neurostimulateurs rechargeables repose sur la durée de vie du premier implant; un neurostimulateur rechargeable peut être remboursé si le premier implant a tenu moins de deux ans. En France par exemple, ce remboursement repose sur les conditions de stimulation à la fin de la période d'essai avant la pose du premier implant et dans d'autres pays, le choix est laissé au prestataire de soins. Cependant, les experts nous confirment que l'estimation de la durée de vie attendue d'un neurostimulateur non rechargeable pour un patient individuel spécifique est difficile à faire du fait qu'elle dépend largement du patient.

8. UTILISATION ACTUELLE ET COÛTS

8.1. Données

Les données collectées pour estimer l'utilisation de la SCS et des IADP en Belgique sont les données individuelles cliniques des hospitalisations classiques et des hospitalisations de jour, liées aux données de facturation de l'assurance maladie et les chiffres globaux (donc non liés au patient) de la consommation d'implants. Les données individuelles ont été rassemblées de 2002 à 2009.

8.2. Systèmes implantés

En Belgique, le nombre d'implants de SCS (primo-implantations et remplacements) a augmenté et est passé de moins de 700 en 2002 à environ 900 en 2009. Le nombre d'implants IADP est resté relativement stable, avec moins de 200 par an. Les neurostimulateurs rechargeables n'ont été lancés que fin 2009 et on ne disposait donc pas de données complètes sur leur utilisation au moment de notre analyse. Les dépenses spécifiques de l'INAMI en matériel ont été de près de € 9 millions en 2009 pour les SCS et de moins de € 2 millions pour les IADP. En 2009, le coût total par implant, matériel et hospitalisation, a été estimé à près de € 20 000 pour un système de SCS rechargeable, à près de € 14 000 pour une IADP et à € 8800 pour un système SCS non rechargeable. La majeure partie de ces coûts concerne le matériel implantable : € 18 500, € 10 100 et € 7500 respectivement. Le coût annuel total directement lié aux implants de neuromodulation pour 2009 a été estimé à près de € 12,5 millions.

L'utilisation de la neurostimulation varie largement d'un hôpital à un autre et d'un endroit à un autre. Des implants de neuromodulation ont été placés dans 55 hôpitaux mais le nombre d'implants par hôpital varie largement et plus d'un quart de leur nombre total a été implanté dans un seul hôpital. La majorité des implants ont été posés en Flandre et plus particulièrement dans les provinces de Flandre orientale et de Flandre occidentale ainsi que dans la province d'Anvers. La majorité des patients implantés vivent dans ces mêmes provinces.

Les chiffres belges de l'utilisation de la neuromodulation sont nettement plus élevés que ceux notés dans les quatre autres pays. En Belgique on implante, par an, 85 SCS et 18 IADP par million d'habitants. Ces chiffres sont nettement plus élevés que dans les autres pays: 54 et 1,4 pour les

SCS et les IADP respectivement aux Pays-Bas, 11 et 1,7 en France (bien que ce dernier chiffre inclue aussi les pompes à baclofène pour d'autres indications que la douleur chronique), 12 et 13 en Allemagne (y compris aussi les pompes à baclofène) et 22 et 1,6 pour le Royaume-Uni.

8.3. Patients et indications

Les informations sur les patients et les indications ont surtout été obtenues par le biais de l'opinion d'experts. Ces informations ont montré que la principale indication de la SCS en Belgique est perçue comme étant le syndrome d'échec de la chirurgie du rachis tandis que les IADP sont principalement utilisées en dernier recours pour les patients souffrant de douleurs réfractaires ingérables autrement. De plus, les patients ont été décrits comme étant d'âge moyen mais avec une espérance de vie raisonnable.

Nos données ont montré qu'environ 60% des patients auxquels on place un implant de neuromodulation sont des femmes et que l'âge moyen est de 52 ans pour les SCS et de 55 ans pour les IADP.

Nous avions pensé que les diagnostics hospitaliers allaient nous permettre d'évaluer les indications et les pathologies sous-jacentes des patients mais les diagnostics ICD enregistrés dans le Résumé Hospitalier Minimum se sont avérés désespérément non spécifiques. Trois des 5 principaux diagnostics étaient non spécifiques et ensemble ils représentaient déjà 60% de l'ensemble des diagnostics principaux. Globalement, on n'a trouvé de code de diagnostic principal de syndrome post-laminectomie que pour 14% (SCS) et 17% (IADP) des patients. Dans les codes de post-laminectomie spécifiques plus de 80% concernait la région lombaire. Les autres codes diagnostics rencontrés ont été difficiles à interpréter avec précision.

Pour les patients chez lesquels on a posé un implant de neuromodulation, l'ensemble des données contenait aussi des informations sur les séjours hospitaliers antérieurs. Pour cette raison, pour les années 2007 et 2008, nous avons pu détecter les chirurgies rachidiennes antérieures au cours des 5 années précédentes. Sur les patients qui ont reçu un implant SCS en 2007 ou en 2008, 32% avaient subi une chirurgie du dos dans les 5 années précédentes (16% des patients ayant reçu un implant IADP).

On a précédemment rapporté qu'en Belgique, l'incidence de la chirurgie rachidienne est plus élevée que dans les pays voisins ce qui peut mener à un nombre relativement plus élevé d'échecs de traitement chirurgical du rachis. Toutefois, il est certes plausible que ce nombre élevé d'échecs soit à son tour lié au taux élevé d'utilisation de la neuromodulation en Belgique mais les données ne permettent pas de le confirmer. Les données indirectes, comme la fréquence plus élevée des chirurgies rachidiennes en Belgique que dans les pays voisins et une distribution régionale de l'incidence des chirurgies rachidiennes similaire à la distribution du recours à la neuromodulation (plus dans le nord du pays que dans le sud) peuvent fournir quelques clés pour comprendre ce problème mais on manque de données détaillées sur les patients pour pouvoir répondre mieux à cette question.

8.4. Durée de vie des piles

Pour étudier la durée de vie des implants, nous avons procédé à une analyse de survie pour estimer la durée de vie des piles des implants. Ces estimations ont varié en fonction des différentes hypothèses modélisées mais dans notre scénario de référence la durée de remplacement médiane des dispositifs SCS entre 2002 et 2008 a été de 3,2 ans. Pour les IADP, la durée médiane de remplacement n'était pas encore atteinte au bout de 5 ans.

9. CONCLUSION

Les données probantes disponibles ne fournissent que des preuves limitées d'efficacité et de coût-efficacité de la neuromodulation. Les indications les mieux documentées pour la SCS sont le syndrome d'échec de la chirurgie du rachis, le syndrome douloureux régional complexe, l'ischémie critique des membres et l'angine de poitrine réfractaire. Pour les IADP, l'indication la mieux documentée est celle des douleurs cancéreuses réfractaires.

La neuromodulation (SCS et IADP) est une technique interventionnelle qui doit être considérée comme la dernière étape possible de l'approche multi-niveaux de la prise en charge des douleurs chroniques réfractaires. Elle ne peut clairement constituer qu'un élément limité au sein d'un plus large éventail d'interventions dans le cadre d'une approche multidisciplinaire de cette prise en charge. En raison du manque de données probantes disponibles, la neuromodulation ne peut être envisagée qu'en dernier recours chez les patients pour lesquels le reste de l'arsenal thérapeutique n'a pas permis d'arriver à un soulagement satisfaisant de la douleur. L'évaluation complète dans un centre multidisciplinaire de la douleur en constitue une condition supplémentaire préalable. Les équipes multidisciplinaires doivent aussi, selon l'origine de la douleur, faire appel à d'autres spécialistes, par exemple à des chirurgiens vasculaires, des cardiologues, des oncologues ainsi qu'aux professionnels paramédicaux spécialisés.

Les indications belges actuellement admises au remboursement ne correspondent que partiellement aux données probantes disponibles et les indications acceptées montrent une grande variabilité entre les pays. Les règles belges actuelles en matière de remboursement sont en pratique, plutôt vagues, et ceci en grande partie parce que les termes *'douleur neuropathique' ouvre la voie à l'interprétation*. De plus, on trouve aussi plusieurs incohérences entre les données probantes et les indications approuvées, ce qui est également le cas à l'étranger. Ces incohérences apparaissent clairement quand on compare les indications approuvées dans les différents pays.

Comme on pouvait s'y attendre, l'utilisation de la SCS et des IADP montre une grande variabilité entre les pays en termes de nombre de dispositifs implantés. Le volume de la neuromodulation est plus élevé en Belgique que dans les pays voisins. La Belgique fait par ailleurs preuve d'une grande variabilité géographique nationale et certains de ses centres sont de réels outliers. Même sans tirer de conclusion sur un quelconque lien de causalité, cette distribution géographique relativement inégale pose question par rapport à l'adéquation des interventions et à l'équité en termes d'accès au traitement.

Etant donné le faible niveau de preuve, il est important que les patients soient informés des incertitudes concernant l'efficacité et la sécurité de ces techniques, la durée de vie limitée des piles des dispositifs et, par conséquent, de la probabilité élevée d'une ré-intervention.

SCIENTIFIC REPORT

SCOPE OF THIS REPORT

The management of severe chronic pain inherently needs a multidisciplinary approach including various medical and para-medical specialties, depending upon the origin of the pain. The management of chronic pain can consist of different types of interventions including analgesic drugs, surgical, physical and psychological therapies, but also several more technical interventional techniques.

The objective of this report is to assess the additional contribution to pain management of one of those additional interventional techniques: neuromodulation.

Neuromodulation, for the purpose of this report, is limited to (1) spinal cord stimulation (SCS) with an implanted stimulator and (2) the implanted intrathecal analgesic delivery pump (IADP). Other techniques, such as deep brain, motor cortex and peripheral nerve stimulation are out of scope. Also the utilisation of intrathecal delivery pumps for non analgesic drugs with indications other than pain management, especially Baclofen for the treatment of spasticity, is out of scope.

More specifically, the aim of this report is:

1. To assess the available evidence from interventional studies on efficacy, safety and cost-effectiveness
2. To describe the current use in Belgium and compare this to the use in neighbouring countries
3. To formulate recommendations for the optimal integration of neuromodulation techniques in the management of chronic pain

Information was gathered through a combination of a systematic review of the peer-reviewed and grey literature, and an analysis of Belgian utilisation data for the years 2002-2009.

1. CHRONIC PAIN AND ITS MANAGEMENT

1.1. Introduction

Pain is a complex phenomenon. It not only involves specific physical sensations, but also has multiple psychological and emotional components. As a consequence the evaluation of pain in an individual is inherently subjective, making comparisons between treatment, and specifically the interpretations of clinical trials more difficult.

Because of the complexity of pain, there have been many discussions between pain specialists about specific definitions. As a result terminology varies across disciplines and countries. It is not the intention of this report to enter this debate or to write another textbook on pain; the scientific literature on this topic is abundant.

For this report we will try to stick to the overall definitions used by the International Association for the Study of Pain (IASP, www.iasp-pain.org) which were last updated in 2012. The IASP claims to be the 'leading professional forum for science, practice, and education in the field of pain'. Membership in IASP is open to all professionals involved in research, diagnosis or treatment of pain. IASP was founded in 1973 and has more than 7000 members in 126 countries, 85 national chapters (including the Belgian Pain Society, BPS, www.belgianpainsociety.org) and 18 Special Interest Groups (SIGs). In this chapter we will reproduce some of these definitions with the permission of the IASP. The full version of the definitions is available at the IASP website.[1]

1.2. General definition of pain

Pain itself was defined by the IASP as: "An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage". Several other aspects, specific of pain, are further underlined in this general definition:

- An individual can experience pain and need appropriate pain-management also when being unable to communicate verbally
- Pain is always subjective and each individual learns the application of the word through experiences related to injury in early life
- Stimuli which cause pain are liable to damage tissue and as a result pain is that experience we associate with actual or potential tissue damage
- It is a sensation in a part or parts of the body that is unpleasant and therefore also an emotional experience
- Experiences which resemble pain but are not unpleasant, e.g., pricking, should not be called pain
- Unpleasant abnormal experiences (dysesthesias) may also be pain but are not necessarily so because, subjectively, they may not have the usual sensory qualities of pain
- People may report pain in the absence of tissue damage or any likely pathophysiological cause and usually this happens for psychological reasons. If they regard their experience as pain, and if they report it in the same ways as pain caused by tissue damage, it should be accepted as pain

This definition avoids tying pain to the stimulus causing it. As a result pain is a very subjective condition and is whatever the patient experiences like it. There is usually no way to distinguish their experience from that due to tissue damage if we take the subjective report. Activity induced in the nociceptor and nociceptive pathways by a noxious stimulus is not pain in itself, which is always a psychological state, even though we may well appreciate that pain most often has a physical cause.

1.3. Specific definitions of pain

We will shortly address the definitions of pain that are most relevant for this report. Our descriptions are based upon the IASP definitions but are no quotes. A more detailed overview can be found in the appendix (see 1.1). The full definitions and a complete overview of them can be found at the IASP website,[1] and in the relevant literature.

1.3.1. Nociceptive pain

This is pain that arises from actual or threatened damage to non-neural tissue and is due to the activation of nociceptors. A nociceptor is a sensory receptor of the peripheral somatosensory nervous system that is capable of transducing and encoding noxious stimuli, i.e. a stimulus that is damaging or threatens damage to normal tissues. Consequences of this encoding may be autonomic (e.g. elevated blood pressure or syncope) or behavioural (motor withdrawal reflex or more complex 'nocifensive' behaviour). Pain sensation is not necessarily implied.

The term *'nociceptive pain'* is intended to contrast with neuropathic pain. It is used to describe pain occurring with a normally functioning somatosensory nervous system to contrast with the abnormal function as seen in neuropathic pain.

1.3.2. Neuropathic pain

Neuropathic pain is caused by a *lesion or disease* of the *somatosensory* nervous system. It is a clinical description requiring a lesion or a disease that satisfies established neurological diagnostic criteria.

The term *lesion* is used when diagnostic investigations reveal an abnormality or when there was obvious trauma. The term *disease* is commonly used when the underlying cause of the lesion is known (e.g. stroke, vasculitis, pancreatitis, diabetes mellitus, genetic abnormality etc…). *Somatosensory* refers to information about the body per se including visceral organs, rather than information about the external world (e.g., vision, hearing, or olfaction).

Neuropathic pain can originate from nerve damage at any point in the nerve pathways from the peripheral nociceptors to the neurons in the brain cortex. Neuropathic pain caused by a lesion or disease of the peripheral somatosensory nervous system is called *peripheral* neuropathic pain. When caused by a lesion or disease of the *central* somatosensory nervous system it is called *central* neuropathic pain.

Neuropathic pain can also be classified on the basis of the aetiology of the insult to the nervous system. Common aetiologies are trauma, ischemia or haemorrhage, inflammation, paraneoplastic or metabolic causes, etc.[2]

The same condition can be painful in some patients and painless in others, but the mechanism behind this is unknown. Therefore a mechanism-based classification of neuropathic pain is not possible. Furthermore, one mechanism can be responsible for many different symptoms, and the same symptom in two patients can be caused by different mechanisms.[2]

Contrary to nociceptive pain, which results from physiological activation of nociceptors by potential or actual tissue injury, chronic neuropathic pain has no beneficial effect.[2]

1.3.3. Paraesthesia

Paraesthesia is an abnormal sensation that might be either spontaneous or evoked. Paraesthesia is used to describe an abnormal sensation that is not necessarily unpleasant. It can be evoked, e.g. by spinal cord stimulation were the paraesthesia coverage in the skin will be used to help determine the optimal placement and settings of the neuromodulation system.

1.3.4. Pain threshold and pain tolerance

The traditional definition of the pain threshold is the minimum intensity of a stimulus that is perceived as painful. However, using the broader general definition of pain it is really the experience of the patient that defines the threshold, whereas the intensity measured is an external event. However, the threshold stimulus can be recognised as such and measured.

Pain tolerance level is the maximum intensity of a pain-producing stimulus that a subject is willing to accept in a given situation. As with pain threshold, the pain tolerance level is the subjective experience of the individual. Again, the stimuli which are normally measured in relation to its production are the pain tolerance level stimuli and not the level itself. Therefore, as with the pain threshold, pain tolerance level is not defined in terms of the external stimulation as such.

1.4. Duration of pain

In its most common manifestation pain is transitory, lasting only until the noxious stimulus is removed or the underlying damage or pathology has healed spontaneously or through therapy. In chronic conditions, however, pain may persist for years. Pain that resolves quickly is called *acute pain*, while pain that lasts a long time is called *chronic pain*.

The distinction between acute and chronic pain is arbitrary and definitions differ and range from an interval of time since onset of 1 to 12 months. Sometimes the term *sub-acute* pain is used for intermediate durations of pain. Another definition of chronic pain is 'pain that extends beyond the expected period of healing'.

1.5. Epidemiology of pain

Pain is a major symptom in many medical conditions and occurs frequently. It also has an important impact on health, health related quality of life (HRQoL) and functioning. Due to the subjective nature of the experience and measurement of pain estimates on incidence and prevalence vary widely depending upon the definitions used. Population surveys provide some insight in the importance of chronic pain.[2]

A British population based study surveyed 6000 randomly selected adults in 3 geographic areas using a postal questionnaire.[3] With a response rate of 52%, the prevalence of any chronic pain was 48% and the prevalence of pain of predominantly neuropathic origin was 8%.

A French postal survey in 30 155 subjects obtained a response rate of 79%.[4] Chronic pain was reported by 31.7% of respondents including 6.9% with neuropathic pain. About 75% of respondents with neuropathic pain reported moderate to severe chronic pain.

A review on neuropathic pain cites several studies reporting relatively high prevalence of neuropathic pain in patients with prolonged back pain.[2] Also post-traumatic and postsurgical nerve injuries and post herpetic neuralgia are common causes of chronic neuropathic pain in the population. Stroke, multiple sclerosis, and spinal cord injury result in neuropathic pain in 8%, 28%, and 67% of patients, respectively. The prevalence of painful peripheral neuropathy was 16% in people with diabetes in the United Kingdom, but despite significant disability, one-third of diabetics with pain had never received any treatment for their neuropathic pain.[2]

In Belgium, the prevalence of pain was also assessed through the regular health interview survey in the Belgian population, using two specific questions from the SF-36. In the last survey (2008) approximately half of the adult population reported some pain in the previous four weeks: 39% complained of light to moderate pain while 12% reported severe pain in the previous four weeks. The prevalence and severity of reported pain are higher in women and increase with age.[5] However, this definition of four weeks does not correspond to the definition of chronic pain as previously mentioned

In a recent report from the Belgian federal ministry of health (FOD–SPF) it was estimated that approximately 8.5% of the population, or nearly 1 million Belgians, might need some form of specialised pain treatment because of chronic pain complaints.[6] However, it should be clear that only a small proportion of this reported number should ever be considered for neuromodulation treatment.

Both in Belgium and internationally, attempts have been made to calculate the global burden of disease of chronic pain and massive financial burdens have been suggested,[7] but these economic evaluations all present methodological problems, making them difficult to interpret and compare.

1.6. Diagnosis and measurement of pain

The diagnosis and measurement of chronic neuropathic pain is a challenge to health care and it is assumed that it is therefore relatively frequent under-diagnosed and under-treated.[2] It is common when investigating neuropathic pain that diagnostic testing may yield inconclusive or even inconsistent data. In such instances, clinical judgment is required to reduce the totality of findings in a patient into one putative diagnosis or concise group of diagnoses.[1]

The subjective nature of pain and the various definitions used also make the objective measurement of pain difficult. For practical purposes and for research several instruments have been developed that attempt to attribute a metric to express the intensity of pain. These instruments include interview questions, postal questionnaires, scoring systems such

as the SF-36 and specific pain grading tools for specific target populations such as children.[8]

For clinical studies the most frequently used generic instrument is the Visual Analogue Scale (VAS) where the patients needs to indicate his/her level of pain by indicating a position along a continuous 100 mm line between two end-points or its numeric variant the Numeric Pain Rating Scale (NPRS). Other instruments attempt to measure the change of pain during treatment or are disease specific for selected types of pain.

1.7. Management of chronic pain

The management of chronic pain is complex, there are no diagnostic gold standards and very often previous therapeutic attempts have failed and the impact of additional psychosocial co-morbidity is often unclear. The impact of those co-morbidities on therapeutic results.is also uncertain.[9]

The management of chronic pain essentially requires a stepwise approach. Several treatment options are available and these should be chosen to best help the patient and using a multidisciplinary strategy including several medical and para-medical disciplines, partially depending upon the pathologic cause of the chronic pain.

Apart from evaluating and treating the underlying cause, this multidisciplinary symptomatic treatment can include the use of adjuvant analgesics, psychological counselling or physical therapy. In a next step, and in a multi-tiered approach several more interventional approaches might be considered, including peripheral analgesics, steroid infiltrations, radiofrequency treatments and other.[10]

Situated at the very end of this multi-tiered approach is neuromodulation, including neurostimulation and intrathecal analgesic delivery. These techniques are the subject of this report.

1.8. Pain management facilities

The IASP has developed sets of guidelines concerning the development of ideal pain treatment facilities, the ethical treatment of test subjects and the development of guidelines for clinical practice. We give a short overview of the main recommendations; more complete information can be obtained from the IASP website.[8]

According to the IASP there is substantial evidence for the effectiveness of multidisciplinary approaches to pain management, because of the complex nature of the pain experience. In their guidelines the IASP differentiates between two modalities for pain management.

1.8.1. Multidisciplinary pain centres

In the definition of the IASP, a multidisciplinary pain centre is distinguished by the broad range of its clinical staff, patient care services, pain conditions treated, and educational and research activities. It should be part of or affiliated with a higher education and/or research institution.

The staff should include clinicians from a variety of medical and other health care disciplines; all clinicians should have expertise in pain management. The clinicians who assess and treat patients in the pain centre should include physicians, nurses, mental health professionals (e.g., clinical psychologist, psychiatrist), and physical therapists. The centre should be able to treat any type of pain problem; thus, there must be a system for obtaining consultation as needed from physicians from disciplines not included on the staff.

A distinguishing feature of a multidisciplinary pain centre is that the clinicians from different specialties work together in the same space and communicate with each other on a frequent and scheduled basis about patients, pain centre policies and procedures, and therapies offered in the pain centre. Care is delivered in a programmed and coordinated manner, and is patient centred, up-to-date, evidence-based, and safe. Clinical activity must be supervised by an appropriately trained and licensed clinical director with expertise in pain management. All the providers in the centre should be appropriately qualified and licensed in their specialty and should be knowledgeable about the contributions of biological, psychological, and social/environmental factors to pain problems.

The centre should serve as a model of excellence for the structure, processes, and outcomes that are essential for high quality pain management. Patient assessment and treatment should be multidisciplinary, involving appropriate specialists as needed, to ensure optimal management of all biomedical and psychological aspects of pain problems. Treatment should aim to improve pain and/or pain management, and also to improve patient physical, psychological, and work and social role functioning. The clinicians should be familiar with all relevant treatment guidelines, and these should be considered in planning clinical activities. The centre staff should routinely collect and summarize data on the characteristics and outcomes (including pain intensity, psychological distress, function, and quality of life) of the patients evaluated and treated, and should engage in continuous quality improvement efforts.

The centre should be committed to advancing and applying current scientific knowledge related to pain, and to disseminating relevant information to patients, other health care providers and organizations, and the public at large, in order to improve the quality of pain management across the continuum of care. As the experts in pain management, the centre's staff is expected to act to improve pain management in local, regional, and national health care services. It is also expected that the centre provides educational activities and training in multidisciplinary pain management for clinicians from multiple disciplines (e.g., physicians of different specialties, clinical psychologists, nurses, physical therapists). Ideally, training should be provided at undergraduate, graduate, and postdoctoral levels.

The centre should be actively engaged in research, ideally playing a leadership role. The centre should contribute to the evidence base for the treatment and management of pain, and train future pain researchers.

1.8.2. Other forms of pain centres

The IASP further describes 'Multidisciplinary Pain Clinics' where research and academic teaching activities are not necessarily included in its regular programs and 'Pain Practices' where a single provider may have a pain practice if he or she is licensed in his or her specialty, has completed specialty pain medicine training or equivalent, and is certified in pain management by the appropriate local or national credentialing organization.

1.9. The most common indications for neuromodulation

Several pain conditions have been suggested as potential indications for adding neuromodulation to the arsenal of chronic pain treatment. Most of these indications are considered as mixture forms of neuropathic and nociceptive pain. The conditions most commonly encountered in literature are *failed back surgery syndrome, complex regional pain syndrome, critical limb ischemia, refractory angina pectoris and refractory cancer pain.*

1.9.1. Failed back surgery syndrome (FBSS)

FBSS is a persistent back pain that may or may not include pain radiating to the leg, after one or more previous back operation(s).[11] It is a mixture of neuropathic and nociceptive low back and leg pain which has failed to respond to anatomically successful surgical treatment.[12]

1.9.2. Complex regional pain syndrome (CRPS)

CRPS is a syndrome occurring as a complication of surgery or trauma, most often in one extremity, although it can also develop spontaneously. A fracture is the most common initial event when it occurs in the upper extremity.[13] It was described first by Sudeck more than one hundred years ago. It is a neuropathic pain syndrome comprising regional pain, and oedema/ vasomotor/sudomotor dysfunction, following noxious event or nerve injury.[12] A distinction is made between CRPS type 1 which is without demonstrable nerve damage, and type 2 with nerve damage.[1, 13]

1.9.3. Critical limb ischemia (CLI)

Ischaemic pain occurs when there is insufficient blood flow for the metabolic needs of an organ. Critical limb ischemia is the ischaemic pain manifestation of peripheral arterial disease (PAD), with chronic ischaemic rest pain or ischaemic skin lesions. It is most commonly seen in patients aged 55 years and older as a result of PAD progression.[14]

1.9.4. Refractory angina pectoris (AP)

AP is a severe ischaemic chest pain, typically as a result of coronary heart disease (CHD). The term refractory angina is used when frequent angina attacks occur and cannot be controlled by optimal drug therapy and or surgery such as coronary artery bypass grafting (CABG) or percutaneous coronary interventions (PCI).[15]

1.9.5. Refractory cancer pain

The treatment of pain in cancer patients depends on the nature of pain which typically is a mixture of nociceptive and neuropathic pain.[16] The neuromodulation technique most commonly mentioned in literature for this indication is IADP to treat pain refractory to systemic analgesics.

2. NEUROMODULATION TECHNIQUES

2.1. Definition of neuromodulation and scope of this report

Neuromodulation is defined by the International Neuromodulation Society (INS) as a technology that acts directly upon nerves. It is the alteration, called *'modulation'*, of nerve activity by delivering an electrical or pharmaceutical agent directly to a neural target area.[a] Neuromodulation can affect every area of the body and those devices and treatments can have an important impact on life.

The most common indication for neuromodulation is as an additional therapeutic tool in the management of neuropathic or mixed neuropathic-nociceptive chronic pain refractory to conventional treatment. This indication is the scope of this report.

However, it has been used to treat many other diseases or symptoms from headaches to tremors and spinal cord damage up to urinary incontinence. There are also different forms of neuromodulation such as deep brain stimulation for Parkinson's disease treatment or sacral nerve stimulation for pelvic disorders and incontinence. A non-exhaustive list can be found in the appendix.

The focus of this report is on two forms of neuromodulation as an add-on in the management of chronic pain: Spinal Cord Stimulation (SCS) with electrical stimulation and implanted Intrathecal Analgesic Delivery Pumps (IADP) for Intrathecal Drug Delivery (IDD). Those are pain management techniques that, contrary to for example neuroablation, attempt to alter the nervous system in a reversible and non-destructive manner.[17]

[a] source http://www.neuromodulation.com

2.1. SCS technology

2.1.1. Definition of SCS

Spinal Cord Stimulation (SCS) for pain management is an invasive therapy that aims at overriding an area of intractable pain of neuropathic origin (as opposed to pain of nociceptive origin) with a localised feeling of numbness and/or tingling (paraesthesia),[17, 18] induced by applying an electrical field over the spinal cord. SCS belongs to a larger group of electrical neurostimulation therapies that in addition comprises Deep Brain Stimulation, Cortical Brain Stimulation, Nerve Root Stimulation (NRS) and Peripheral Nerve Stimulation (PNS),[19] all of which are outside the scope of this evaluation.

2.1.2. History of SCS

2.1.2.1. Early history of electrical pain management

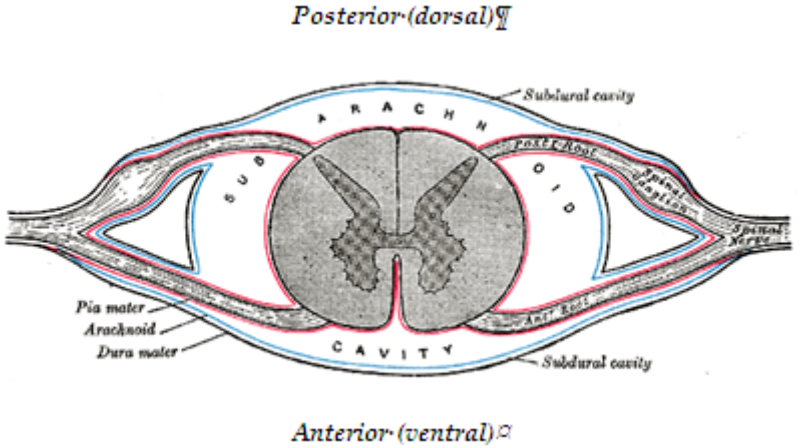
It is believed that electric stimulation has been in use for the treatment of pain, since the time of ancient Egyptians.[19] As early as the first century AD, Scribonius Largus, the court physician to Roman emperor Claudius, reported that in ancient Greece, pain was relieved by standing on an electrical fish at the seashore.[19, 20]

From the sixteenth through the eighteenth century, various electrostatic devices were used for headache and other pains. Among the proponents of this method for pain relief was Benjamin Franklin. A device called the electreat was used for pain control in the nineteenth century. It was not portable, had limited control of the stimulus, but survived into the twentieth century. Additional information about these devices can be found at www.electrotherapymuseum.com.

2.1.2.2. Recent history of spinal stimulation

In 1967, the inhibition of pain by *subdural* (=underneath the 'dura mater', see Figure 1) electrical stimulation of the spinal cord was first reported.[21, 22] A unipolar electrode was placed directly on the spinal cord through a surgical procedure. The theory behind this technique was based largely on the so-called *'gate control theory of pain'*, proposed two years earlier by Melzack and Wall.[23]

Figure 1 – Diagram of a transverse section of the medulla spinalis and its meninges



Source: Henry Gray, Anatomy of the Human Body, 1918

Although good pain relief was achieved, *subdural* spinal cord stimulation resulted in complications by fibrosis and morbidity.[24-27] This led a few years later, to the development of *epidural* (=on the surface of the 'dura mater') spinal cord stimulation, whose analgesic properties were first demonstrated by Shimoji and colleagues in 1971.[20] This quickly led in 1975 to the placement of an epidural stimulator,[17, 25] and the development of small multipolar ring electrodes on a thin flexible lead allowing for a less invasive, percutaneous implantation.[28] The ability to implant electrodes without the need for a surgical laminotomy (also called laminectomy) increased the number of practitioners capable of implanting SCS systems.[17] Current SCS systems evolved from there. (see section 2.1.6 for a description.)

However, one year earlier in 1974, the first patient-wearable and battery-operated external device for Transcutaneous Electrical Nerve Stimulation (TENS) was patented in the United States.[29] It was initially used for testing the tolerance of chronic pain patients to electrical stimulation with skin electrodes prior to implantation of electrodes in the spinal cord.[30] Although

initially intended for tolerance testing only, many patients received satisfactory pain relief from TENS and never returned for an implant. Towards the end of the seventies, this resulted in TENS becoming a pain relief therapy on its own. However, TENS as a therapy on its own is outside the scope of this report.

2.1.3. Mechanism of SCS action

2.1.3.1. Poorly understood mechanisms

The precise mechanism of pain modulation is poorly understood. However, several theories were proposed including the previously mentioned gate control theory,[17, 23, 31] or the interaction with neurotransmitters through their effect on the autonomic nervous system.[31, 32] Furthermore, it has been speculated that for ischaemic pain, analgesia also seems to be related to the restoration of microcirculatory blood flow.[19, 33, 34] More recently, studies using functional magnetic resonance imaging during the application of SCS and other stimuli have shown the activation of specific cerebral regions during the application of these stimuli.[35]

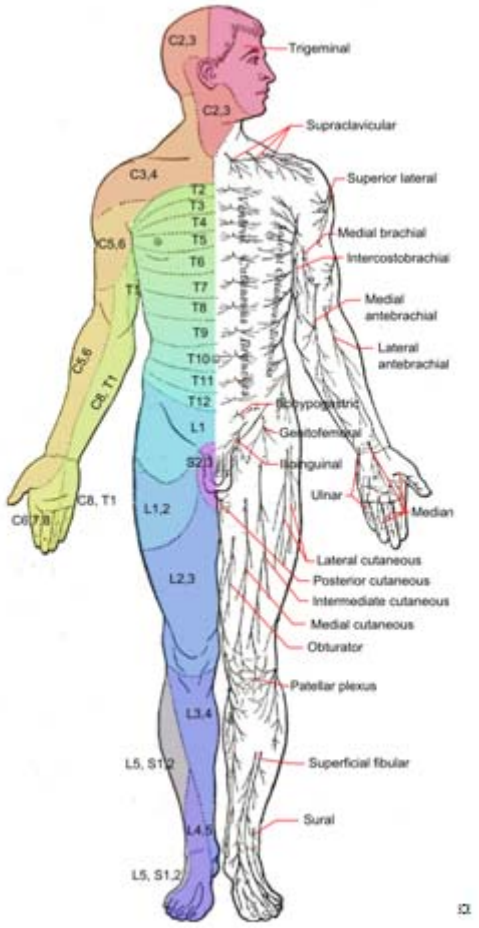
2.1.3.2. Mainly for chronic neuropathic pain

SCS is even more complex in that it is effective for chronic but not acute pain,[17] for neuropathic and sympathetically mediated pain, but not nociceptive pain.[17, 31, 36]

2.1.3.3. Level of stimulation

The target level for stimulation is typically several spinal levels higher than the spinal nerves of the dermatome or dermatomes (Figure 2) to be covered.[17, 19] Spinal cord stimulation produces a feeling of numbness and tingling, called paraesthesia. For SCS to be effective, paraesthesia needs to be superimposed over the area of pain.[18] This is called the *'area of concordant paraesthesia'*.[36] However, even when paraesthesia superimposition is achieved, this does not necessarily elicit pain relief.[17, 37]

Figure 2 – Ventral view of dermatomes and major cutaneous nerves



Source: http://commons.wikimedia.org/

2.1.3.4. Potential advantages of multiple electrodes SCS

For SCS to be effective, the area of paraesthesia must overlap the area of pain. Selection of leads depends on which arrangement will give the best paraesthesia coverage of the painful area. At present up to 16 electrodes can be stimulated by one implantable pulse generator and they are typically inserted in arrays of 4 or 8 electrodes.[19]

2.1.4. Claimed advantages of SCS

The following advantages of SCS are often claimed:[19]

- SCS is a useful (additional) option when more conventional therapies fail[38]
- Unlike nerve ablation, SCS is reversible
- SCS may offer analgesia on demand: anywhere, anytime. This makes the patient feel more in control of his condition
- SCS results in a better quality of life and patient morale
- SCS can reduce the use of pain medications[39] and may hence reduce or avoid some side effects of pharmacotherapy
- SCS therapy does not restrict daily activities

2.1.5. Disadvantages of SCS

The following disadvantages of SCS are often mentioned:[19]

- SCS is not curative for the underlying condition[12]
- SCS appears to be effective in only about 50 to 70% of the cases even for accepted indications
- SCS is an invasive procedure and hence, even if rare, may result in severe adverse events such as infection, haematomas (subcutaneous or epidural), seroma, dural puncture, Cerebrospinal Fluid (CSF) leaking, paraplegia, allergic response, etc.[17]
- SCS is more expensive than conventional medical treatment[40]
- SCS is often not a stand-alone therapy[12]
- SCS requires regular follow-up checks
- SCS relies on implanted electrical devices that may migrate, erode, disconnect or fail
- SCS may interact or be incompatible with a number of other medical therapies and diagnostics: neuraxial blockade (including epidural anaesthesia), diathermy, pacemakers, magnetic resonance imaging (MRI) and therapeutic ultrasound. Those interactions may result in unexpected changes in stimulation, serious patient injury or death. It may also lead to failure of the device

2.1.6. The SCS system

2.1.6.1. Electrodes

The epidural electrodes consist of an array of leads (4, 8 and up to 16 electrodes) and they can be of the percutaneous type or the paddle type. The latter need to be inserted through a laminotomy.[19]

A patient could also have up to two 8-electrode leads or up to four 4-electrode leads. Those electrodes can be placed parallel to each other or at different vertical sites. Those different arrangements are intended to best cover the painful area.[19]

The advantage of the percutaneous electrodes is that they are easier to insert with less invasive techniques and with less risk. Claimed advantages of paddle type electrodes include having lower stimulation amplitudes needed (and therefore longer battery life) because of the larger contact surfaces (Kanpolat in a comment on Aló[24]). They are also claimed to present reduced lead migration.[19]

Different electrode designs and configurations are or have been available on the market. Each of these come with specific claimed benefits and inconveniences. However, it was reported that there is little evidence to support that the technically more advanced types of SCS systems are more effective than the more simple quadripolar percutaneous electrodes.[41] An evaluation of different electrode types is without the scope of this technology assessment.

2.1.6.2. Lead extensions

Lead extensions serve to connect the various types and numbers of electrodes with the implantable pulse generator (IPG) through a subcutaneous tunnel. They are available in different lengths and can be shortened as desired to fit an individual patient.

2.1.6.3. Stimulation sources

Several stimulation sources exist depending upon the needs of the patient. The generator is either an external pulse generator for testing, an implanted pulse generator with its own battery or only a radio frequency (RF) receiver with an external stimulator.

The *external pulse generator* is used during the stimulation test period to assess the effectiveness of the SCS therapy in a given patient.

The *implantable pulse generator (IPG)* is implanted subcutaneously. The IPG has its own battery. Apart from IPGs with classical batteries, some IPGs have a rechargeable battery which can be charged externally through a wireless power charger so that it does not need to be replaced as frequently because the battery is empty.

The implantable RF receiver, less used nowadays, is externally driven by a transmitter from which it gets its power and pulses. This external transmitter has a battery which can be easily replaced without requiring new surgery. RF receivers have traditionally been used for patients that require high power settings that would quickly deplete a classic battery driven IPG.[19]

2.1.6.4. Electrical properties of stimulation sources

Various current, voltage and waveforms configurations are possible. Various spinal cord stimulators are available, some with constant current, variable voltage or with constant voltage, variable current. There is currently no consensus over the relative efficacy of their respective current and voltage configurations.[19]

2.1.6.5. Battery longevity

The battery longevity for non-rechargeable stimulators varies, depending on type and stimulation settings, but it is claimed that an IPG should last between two and seven years.[42] The longevity of a rechargeable stimulator is frequently, but not always, limited to nine years.

2.1.6.6. Physician programmer

The treating physician has a programming device that can be used to modify a wide range of stimulation settings of the IPG.[19]

2.1.6.7. Patient remote control

Also the patient is provided with a remote control to turn on and off the stimulator. Depending upon the device and the preference of the treating physician the patient can also change some of the settings. [19]

2.1.6.8. Manufactures of SCS systems

In Belgium SCS systems are marketed by:

- Medtronic
- St Jude Medical (formerly ANS)
- Boston Scientific
- Nevro

2.1.7. SCS procedures

2.1.7.1. Selection of the level of stimulation

As explained previously, the target for stimulation is typically several spinal levels higher than the spinal nerves of the dermatome or dermatomes to be covered.[17, 19]

2.1.7.2. Electrode selection

For the SCS to be effective, the area of paraesthesia must overlap the area of pain.[37] Electrode selection should be in function of which arrangement will give best paraesthesia coverage over the painful dermatome(s).[19]

2.1.7.3. Electrode placement

SCS procedure involves careful placement of electrode(s) in the epidural space at the desired level(s). The position of the electrodes is controlled through radioscopy. Stimulation during the intervention is undertaken to confirm appropriate paraesthesia. This procedure is carried out under local-anaesthesia to allow for the patient to react to this test-stimulation during the procedure. After confirmation the electrodes are anchored and an extension lead is tunnelled and connected to an external pulse generator that is then programmed for a specific pattern of stimulation.[19]

2.1.7.4. Stimulation trial

The stimulation trial period may vary in time, but in the USA it is reported to be between 5–7 days.[19] In Europe those trial periods tend to be longer (see chapter 6 on the international comparison). During this trial period an external pulse generator is used to assess the effectiveness of the SCS therapy in a given patient.

2.1.7.5. Implantation of permanent stimulator

If the stimulation trial is satisfactory (i.e. the results of pain relief are satisfactory) the procedure can be finalised with the positioning and implantation of the permanent stimulator, connecting it to the electrodes and programming the system for the optimal pattern of stimulation.[19]

The IPG or the RF unit is usually implanted in the lower abdominal area or in the gluteal region. It should be in a location that patients can easily access with their dominant hand for adjustment of their settings with the patient-held remote control. The IPG battery life will largely depend on the power settings utilised, but the newer non-rechargeable IPG units are claimed to generally last several years at average power settings.[19]

Programming involves selecting the electrode stimulating configuration and adjusting the amplitude, width and frequency of electrical pulses. Programming partly depends on individual preferences: some patients prefer a low frequency beating sensation whereas others prefer high frequency buzzing.[19]

Selection of the lowest possible setting on all parameters is important in conserving battery life in non-rechargeable SCS devices. Cycling of stimulation is also used to save battery life. Changing programming parameters may be needed during follow-up.[19]

2.2. IADP technology

2.2.1. Definition of IADP

An Intrathecal Analgesic Delivery Pump (IADP) for the management of chronic pain is an implantable device for delivering analgesic drugs (primarily opiates) intraspinally. The same device may also be used to deliver Baclofen for the treatment of spasticity but this application is beyond the scope of this report.

The term intrathecal refers to something being introduced into or occurring in the space under the arachnoid membrane (see Figure 1), a space containing the cerebrospinal fluid (CSF).

2.2.2. History of IADP

Analgesic Intrathecal Drug Delivery (IDD) has been around for approximately 30 years, after the discovery of opioid receptors in the central nervous system (CNS) and more specifically in the spinal cord, thereby providing an alternative delivery route for opiates in both cancer pain and chronic non-malignant pain (CNMP).[17, 43]

2.2.3. Mechanism of IADP action

The assumed advantage of IDD over systemic administration is that adequate concentrations of opiates at the dorsal horn can only be achieved by high doses when given systemically, while intrathecal delivery is a means of achieving enhanced therapeutic effects with much smaller doses by automatically delivering the analgesic drug much nearer to, and at the desired level, of the central nervous system receptors.[43] It has been estimated that intrathecal administration can reduce the dose by a factor 100.[44]

An IADP is a medical device used to automatically deliver these small quantities of medication directly to the spinal fluid at a desired location. The aim is to reduce the side effects often associated with the systemic use of higher doses.[17, 43]

Those systems are implanted and use a pump to deliver the medication to the spinal canal by way of small implanted tubes called catheters. Some pumps are programmable while other types deliver medication at a constant flow rate.

The pump with its drug reservoir is implanted under the skin, most often at the lower abdomen, and can be refilled by inserting a small needle through the skin and into the refill port. Bolus administration of analgesics (the administration of a single, larger dose) can be made either through a specific bolus port or with the remote control for programmable IADPs.

2.2.4. Claimed advantages of IADP

The following advantages of IADP are often claimed: [17, 43]

- Increased efficiency when opiates are delivered directly to the target sites in the CNS
- As a consequence, a drastic reduction of analgesics dosage becomes possible compared to systemic administration
- A potential reduction of physiologic side effects
- A reduced risk of inappropriate dosage or abuse

2.2.5. Disadvantages of IADP

The following potential complications with IADP are mentioned in literature:[17, 43]

- Complications from the surgery, although rare, can have major implications when they occur
- Complications from surgery include infection, excessive bleeding during surgery, spinal cord injury during the catheter placement and catheter fracture or migration
- After successful placement of an IADP system and anywhere during follow up the device can stop working properly wich may lead to severe withdrawal syndromes
- Error during refill (pocket fill) or pump malfunction might lead to acute overdoses, which is a medical emergency that can lead to death

Apart from device related complications, the intrathecal delivery of opioids has also been reported to be associated with several drug related complications including general endocrine complications,[45], increased mortality rates[46, 47] or the development of inflammatory mass lesions at the tip of the catheter.[48]

The choice of the specific drug for intrathecal delivery is without the scope of this technology assessment.

2.2.6. The IADP system

2.2.6.1. Intrathecal catheter

Catheters are available in different lengths to adapt for various patients and placements. The catheter is implanted in the intrathecal space and tunnelled subcutaneously to a pocket over the abdomen. At the moment of placement of the catheter it is usually connected to a subcutaneous injection port connected to an external pump for a test period.[43]

2.2.6.2. IADP

After a successful test period (one to several weeks), the external pump is replaced by an implanted IADP, either a constant flow pump or a programmable variable rate pump.

Constant flow rate pumps are generally less expensive than variable flow rate delivery systems but lack flexibility. Because the rate is fixed, the concentration of the drug within the pump has to be changed to increase or decrease the dose of a drug. An advantage is that they have larger reservoir volumes, so larger volumes can be delivered or the interval between refills can become longer.[43] Another advantage is that they are not battery powered so they, in the absence of other problems, function during the whole patients' lifetime.

Variable rate delivery systems are more expensive. However, they allow for more flexibility in the management of chronic pain through easy dose alteration. They also have facilities for the administration of a bolus and for patient activated bolus programmes.[43]

2.2.6.3. Battery longevity

Fixed rate delivery systems are not dependent on an electrical power source since they are driven by expanding gas. Variable rate IADP's are battery driven and battery life is claimed to vary from 4-8 years.[43] At the end of battery life they need to be replaced.

2.2.6.4. Physician programmer

For the programmable variable flow rate IADPs the physician has a physician programmer that allows reading and changing settings of the system, to print patient records and store previous settings.

2.2.6.5. Patient remote control

For the programmable variable flow rate IADPs the patient also receives a remote control. With this device the patient can adjust the delivery of medication to his needs within the limits set by the physician.

2.2.6.6. Manufacturers

In Belgium the following manufacturers actively market their IADP systems:

- Medtronic
- Johnson & Johnson Medical (formerly Codman)

2.2.7. IADP procedures

2.2.7.1. Trial

Before implanting a permanent system patients should go through a trial for efficacy *('can it work?')* or toxicity *('is it safe?')*.

2.2.7.2. Placement of the intrathecal catheter

Catheter placement is often performed under total anaesthesia since no cooperation from the patient is needed during the intervention, in contrast with SCS electrode placement. Catheter position is controlled through radioscopy and when well-positioned it is fixated. Depending on whether a test period is required, the catheter is either tunnelled and connected to an IADP or connected to a subcutaneous injection port that will be subsequently connected to an external pump during the test period.[43]

2.2.7.3. IADP implantation

After a successful trial period with an external pump, a permanent IADP is implanted and connected to the catheter. Afterwards the IADP is programmed (if available).

3. EFFECTIVENESS AND SAFETY

3.1. Introduction

This chapter deals with the efficacy, effectiveness and safety of implantable neuromodulation devices. The chapter is intended to be concise but detailed information can be found in the appendix.

For the systematic literature review of evidence from interventional studies, we only included randomised controlled trials (RCTs) or systematic reviews of RCTs. Observational evidence on effectiveness and safety is assessed in the discussion section.

3.2. Methods

3.2.1. Types of studies

RCTs or systematic reviews of RCTs were included. All searches were performed in the first two months of 2012.

3.2.2. Patients included

Adults with intractable pain (including angina or lower leg ischemia) not satisfactorily responding to optimal medical and paramedical treatment (further referred to as *'optimal medical treatment').*

3.2.3. Types of interventions

The experimental intervention should be Neuromodulation, either implanted Medullar Electrical Stimulation (Spinal Cord Stimulation, SCS) or an Intrathecal Analgesic Delivery Pump (IADP) as an implanted device with or without optimal medical treatment. Neuroablation as intervention therapy was excluded. The control arm should be optimal medical treatment, with or without neuroablation. The control arm should exclude placebo only, or any other type of non-active comparator (e.g. no treatment, waiting list) without any other type of pain medication or specific drug treatment, as applicable.

3.2.4. Types of outcome measures

3.2.4.1. Primary outcomes

The primary outcome was satisfactory pain relief assessed through inherently subjective pain measurement scales.

3.2.4.2. Secondary outcomes

Secondary outcomes were the assessment of Health Related Quality of Life (HRQoL), physical and functional abilities (e.g. activities of daily living, medication intake, etc.), and anxiety and depression.

3.2.4.3. Adverse events

All reported adverse events were described.

3.2.5. Search strategy for the systematic literature review

EMBASE (through OVID®), Pubmed (through Medline) and the Cochrane Library were searched for relevant systematic reviews, health technology assessment reports and RCTs. We used text words and indexed terms for chronic or intractable pain and for neuromodulation. Filters for systematic reviews and RCTs were used for Embase and Pubmed. Searches were limited to studies published in English, French, German, Dutch or Spanish, from 2002 onwards. The full search strategy is given in the appendix. An iterative approach was used; we first searched for systematic reviews or health technology assessment reports based on a systematic review. Then, if systematic reviews were identified, more recent RCTs would be searched for. If no systematic reviews or HTA reports were identified the search was to be extended to RCTs.

3.2.6. Reference tracking

The references of selected systematic reviews, and of narrative reviews with a systematic search, were tracked for relevant studies.

3.2.7. Data collection and analysis

3.2.7.1. Selection of studies

Two reviewers independently selected suitable studies for inclusion. The titles and abstracts of studies identified by searching electronic databases were assessed to determine if an article was eligible. An article was rejected when the title and abstract contained sufficient information to determine that it did not meet the inclusion criteria. The full papers of all remaining articles were retrieved. Selection criteria are according to the type of studies, type of participants, type of interventions and type of outcomes specified. In addition an article needed to be a RCT or a systematic review (systematic search, quality appraisal and systematic data synthesis) of RCTs. Disagreements between reviewers were to be resolved through discussion.

If more than one systematic review were to be retrieved, and if their results were to be discordant, a selection of one review (the most relevant, highest quality, most recent, etc.) was intended according to the algorithm proposed by Jadad et al.[49] The selection process would be described in a flow chart and was intended to include the reasons for not selecting papers.

3.2.7.2. Data extraction and management

Data were abstracted by one researcher, and numerical data were checked by a second researcher. Data were extracted from all relevant publications in a standard format. Key components of the data extraction included:

- Information about study reference(s) and author(s)
- Study characteristics
  - Study methods
  - Participants
  - Interventions
  - Outcome measures and results

Outcome data were extracted if they reflected mean differences between groups at follow up, not the differences in mean change within groups.

3.2.7.3. Assessment of methodological quality

Selected studies were judged on their methodological quality by two researchers independently, using the Cochrane´s risk of bias tables for RCTs,[50] and the AMSTAR checklist for systematic reviews.[51] Disagreements between reviewers were resolved through discussion.

3.2.7.4. Data analysis

Data were described in evidence tables and text, per patient subgroup. Data were (re)calculated from primary data when needed. *STATA 10.1* was used to calculate missing p-values for between-group differences, if possible.[52] This was done for two studies.[53, 54]

'Comprehensive Meta-analysis 2.2.048' was used to recalculate meta-analyses,[55] if controversies between different meta-analyses would arise. This was done for the main meta-analysis (limb survival) of Klomp 2009 and Ubbink 2005-2009.[56-58]

Uncertainty of results is expressed using p-values or by giving confidence intervals (CI) around point estimates. Unless otherwise indicated, confidence intervals in this chapter are 95% CI.

3.2.7.5. Assessment of the strength of the body of evidence

GRADE was used to describe the strength of the body of evidence.[59] Each outcome of selected systematic reviews, or of a single individual trial, was graded by two researchers independently. Disagreements between reviewers were resolved through discussion. The reasons for up-/downgrading were documented.

3.3. Results

3.3.1. Overview of the search and selection process

We identified 17 systematic reviews on SCS (Table 23 in the appendix),[12, 34, 56-58, 60-73] and 6 systematic reviews on IADP (Table 24 in the appendix).[66, 74-79]

Overall, the 17 systematic reviews on SCS included 17 RCTs (eight in patients with angina, one in patients with complex regional pain syndrome (CRPS), one in patients with diabetic neuropathy, two in patients with failed back surgery syndrome (FBSS) and five RCTs in patients with limb ischemia). Only three of the systematic reviews applied meta-analysis (Table 23).[56-58, 71]

The six systematic reviews on IADP included two RCTs (Table 24). Additionally, three other RCTs were identified that concerned a therapy switch from morphine to ziconotide in patients with chronic refractory pain (cancer and non-cancer pain) with a intrathecal administration system in place, either implanted or external prior to the study.[80-82] Since those were short term studies and were actually a drug trial rather than a trial on IADP those were not included in this review.

Because systematic reviews outnumbered RCTs for most SCS and IADP populations –except for patients with critical limb ischemia– and because selection criteria of systematic reviews frequently differed from our pre-defined selection criteria, we decided to use the RCT results directly and re-apply our selection criteria to these trials. Twelve RCTs on SCS and one RCT on IADP were compatible with our inclusion criteria. Five RCTs on SCS were excluded (three trials included patients that were already on SCS; two trials had no controls and thus were not RCTs) and one RCT on IADP was excluded (patients were their own controls) (see Table 25 and Table 26 in the appendix for an overview).

For SCS we then decided to include the two systematic reviews on critical limb ischemia which included all five RCTs in this population, all in line with our own inclusion criteria (Klomp 2009[56] and Ubbink 2005-2009[57, 58]) as well as the remaining seven RCTs in other patient populations still in line with our inclusion criteria (four RCTs in angina patients; one RCT in patients with complex regional pain syndrome; and two RCTs in patients with failed back surgery syndrome), More details are shown in Table 25 and Table 26 in the appendix.

For SCS we then searched for RCTs since the last search date (August 2007) of the review of Simpson et al.[12] and for RCTs on IADP since the last search date (December 2010) of the review of Hayek et al.[74] We found ten additional publications of RCTs previously identified (see also Table 25) and one recent RCT on SCS in angina (Lanza 2011[83]) that was not included in the systematic reviews.

An overview of the whole search and selection process is given in Figure 15. A global assessment of the methodological quality of the selected RCTs (risk of bias) and the selected systematic reviews (AMSTAR checklist) is given in Table 27 and Table 28 in the appendix. These assessments will be further discussed with the results by indication.

3.3.2. Spinal cord stimulation in patients with failed back surgery syndrome (FBSS)

Two RCTs evaluated the effectiveness of SCS in patients with failed back surgery syndrome (North 2005[39] and Kumar 2007[84, 85]).

3.3.2.1. Sample sizes and setting

One trial randomised 50 patients in a single centre in the United States (North 2005[39]). The other trial randomised 100 patients in multiple centres worldwide (Kumar 2007[84, 85]) (Table 33 in the appendix).

3.3.2.2. Participants

The trial by North et al. [39] included patients with surgically remediable nerve root compression and concordant complaints of persistent or recurrent radicular pain, refractory to conservative care, who had had one or more lumbosacral spine surgeries. Patients with a disabling neurological deficit in the distribution of a nerve root or roots caused by surgically remediable compression, a radiographically demonstrated critical cauda equina compression, or radiographic evidence of gross instability necessitating fusion were excluded.

The trial by Kumar et al. [84, 85] included patients with neuropathic pain of radicular origin predominantly in the legs, of an intensity ≥ 50 mm VAS, for six months or longer after one or more anatomically successful surgeries for herniated disc (Table 33).

3.3.2.3. Interventions

The trial by North et al. [39] compared SCS to repeated lumbosacral spine surgery; the trial by Kumar et al. [84, 85] compared SCS to conventional medical management (CMM), see Table 33.

3.3.2.4. Outcomes

The outcomes were crossover to the other treatment group, ≥50% pain relief and treatment satisfaction, stable or decreased opioid use and ≥50% leg pain relief (Table 33).

3.3.2.5. Risk of bias

The risk of bias through random sequence generation, allocation concealment, incomplete outcome data or selective reporting was assessed as ´low´ for both studies. The risk of bias through the blinding of participants, personnel or outcome assessors was assessed as ´high´. Both trials were industry sponsored (Table 27).

3.3.2.6. Effects of interventions

There was low quality evidence from the North et al. trial that SCS was more effective than repeated lumbosacral spine surgery at three years for achieving ≥50% pain relief and treatment satisfaction (47% vs 12%, p<0.01), stable or decreased opioid use (87% vs 57%, p=0.03) and because of less cross-over to the other treatment group (5 vs 14, p=0.02).[39] All four reported adverse effects in this trial occurred in the SCS treatment group (one infection and three hardware revisions) (North 2005[39]).

There was low quality evidence from the Kumar et al. trial that SCS was more effective than CMM in providing ≥50% leg pain relief at six months (48% vs 9%; p<0.01) and at 24 months (37% vs 2%; p<0.01). [84, 85] At six months SCS patients experienced lower levels of back pain (difference in means: -11.0 mm VAS score; 99% CI: -25.0 to 3.0, p<0.01) and leg pain (difference in means: -26.7; 99% CI: -40.4 to -13.0; p<0.01), enhanced health-related quality of life on seven of the eight dimensions of the SF-36 (p≤0.02), superior function (Oswestry disability index, p<0.01), and greater treatment satisfaction (p<0.01) (p-values were adjusted for base-line values and covariates). Analgesic drug intake was similar in both groups, except for anticonvulsant intake (26% vs 50% (p=0.02)). Main non-drug therapy was similar in both groups except for massage and transcutaneous electrical nerve stimulation, which was not used in the SCS group (p≤0.05). More SCS patients were satisfied with pain relief and agreed with their treatment (p<0.01). Rates of return to work did not differ between the groups (11% vs 3%; p = 0.36). Of the 84 patients who received an electrode in this trial (either during the screening trial or as a result of system implantation), 27 (32%) experienced a total of 40 device-related complications in the first year. For 20 (24%) patients surgery was required. Principal complications were electrode migration (10%), infection

or wound breakdown (8%), and loss of paraesthesia (7%). In total, 18 (35%) of the SCS group and 25 (52%) of the CMM group experienced one or more non-device-related events, most commonly a drug adverse event or the development of new illness, injury, or condition (Kumar 2007[84, 85]) (Table 33 and Table 34).

3.3.2.7. Discussion

Two small non-blinded trials evaluated SCS in patients with failed back surgery syndrome. In the trial that evaluated SCS versus repeat lumbosacral spine surgery 39 patients refused randomisation and opted for repeat surgery. The p-values for between-group differences in means were adjusted for base-line values and covariates in this study. When we calculated unadjusted p-values these were also significant for all reported significant outcomes (back pain: p=0.04; leg pain: p<0.01; health-related quality of life on seven of the eight dimensions of the SF-36: p≤0.02; Oswestry disability index: p<0.01).

3.3.2.8. Conclusion

There was low quality evidence that SCS was more effective than repeated lumbosacral spine surgery at three years in relieving pain and providing treatment satisfaction, stable or decreased opioid use and in less cross-over to the other treatment group.

There was low quality evidence that SCS was more effective than CMM at six months in providing leg pain relief, lower levels of back pain and leg pain, quality of life and superior function.

3.3.3. Spinal cord stimulation in patients with complex regional pain syndrome (CRPS)

One RCT evaluated the effectiveness of SCS in patients with complex regional pain syndrome (Kemler 2000[86-88]).

3.3.3.1. Sample sizes and setting

This one trial was a single centre trial, conducted in the Netherlands, and included 54 patients (Table 31 in the appendix).

3.3.3.2. Participants

Participants met the diagnostic criteria for reflex sympathetic dystrophy established by the International Association for the Study of Pain with impaired function and symptoms beyond the area of trauma. Disease was clinically restricted to one hand or foot and affected the entire hand or foot, had lasted for at least 6 months with no sustained response to standard therapy (6 months of physical therapy, sympathetic blockade, transcutaneous electrical nerve stimulation, and pain medication). In addition, the mean VAS had to be 50 mm or more on a 100 mm scale (Table 31).

3.3.3.3. Interventions

The experimental group received SCS plus physical therapy, whereas the control group received physical therapy only (Table 31).

3.3.3.4. Outcomes

Reported outcomes were the mean VAS score, a reported outcome of ´much improved´ for the global perceived effect, quality of life (Euro-QoL) and adverse effects (Table 31).

3.3.3.5. Risk of bias

This trial was assessed as having a ´low´ risk of bias in the domains of random sequence generation, allocation concealment, incomplete outcome data, selective reporting and other bias (industry funding). For the domains blinding of participants and personnel and blinding of outcome assessment the risk of bias was assessed as ´high´ (Table 27 in the appendix).

3.3.3.6. Effects of interventions

There was low quality evidence that patients who received SCS plus physical therapy had less pain at 12 months compared to patients who received physical therapy alone (mean VAS 44 (SD: 28) vs 71 (SD: 22) mm; p<0.01). In addition, there was low quality evidence that patients who received SCS plus physical therapy more often had a *'much improved´* global perceived effect (39% vs 6% at 6 months; p<0.01), and scored better on the EuroQoL quality of life questionnaire (0.43 (SD: 0.32) vs 0.22

(SD:0.29); p=0.02). At two years 38% of patients with SCS had needed a re-intervention, mainly for electrode migration and pain. Two patients underwent permanent SCS removal due to recurrent rejection and relapsing ulcerative colitis subscribed to the system, respectively. In all patients some side effects were reported, see Table 31 and Table 32 in the appendix.

3.3.3.7. Discussion

This small trial evaluated SCS in patients with complex regional pain syndrome. Changes in functionality and health related quality of life at 6 and 24 months were reported as within-group changes (pre-post change) and were not reported by us (all were non-significant). Adverse events were well described and important.

3.3.3.8. Conclusion

There was low quality evidence that SCS plus physical therapy was more effective in reducing pain than physical therapy alone in patients with complex regional pain syndrome. All patients had side effects and 38% of patients needed a re-intervention within 2 years.

3.3.4. Spinal cord stimulation in patients with diabetic neuropathy

The only study we identified for this indication was excluded since it was no RCT and there was no control treatment beyond the SCS test period (Tesfaye 1996[169]).

3.3.5. Spinal cord stimulation in patients with critical limb ischemia (CLI)

Two systematic reviews with meta-analyses evaluated the effectiveness of SCS in patients with critical limb ischemia (Klomp 2009[56]; Ubbink 2005-2009[57, 58]). The review by Ubbink and Vermeulen included one non-RCT, which we do not discuss here.

3.3.5.1. Sample sizes and setting

Both systematic reviews (Klomp 2009[56] and Ubbink 2005-2009[57, 58]) included the same five randomised clinical trials, all of which had small sample sizes. The 2005 Cochrane review by Ubbink et al. additionally included a CT by Amann[89] and was updated in 2009. For the purpose of this review we deleted the data from this CT.

The largest trial in those reviews (ESES) included 120 participants with critical, inoperable leg ischemia.

3.3.5.2. Participants

The review of Klomp[56] included a total of 332 patients in its meta-analyses.[56] Because the systematic review of Ubbink and Vermeulen[57, 58] excluded patients with leg ischemia solely due to non-atherosclerotic vascular diseases, like Raynaud's disease or Buerger's disease, the total number of participants was slightly lower (321, since 11 patients with Buerger's disease were excluded and since we also excluded results from the Amann[89] CT). All trials were conducted in Western European countries (Belgium, Germany, the Netherlands (2 trials) and Sweden) (Table 35).

3.3.5.3. Interventions

All five randomised trials compared SCS with or without conservative treatment to conservative treatment alone (Table 35 in the appendix).

3.3.5.4. Outcomes

The outcomes in the review by Klomp et al. were mortality and amputation incidence. The outcomes in the review by Ubbink and Vermeulen were amputation incidence, reaching Fontaine stage II,[b] reaching Fontaine stage III, ulcer healing and hypertension, quality of life and adverse effects. Outcomes were evaluated from 1 year to two year post-randomisation (Table 35).

[b] The Fontaine classification is a clinical classification of peripheral artery disease, ranging from Fontaine stage I (asymptomatic), stage II (Intermittent claudication), stage III (rest pain) to stage IV (ischemic ulcers or gangrene).

3.3.5.5. Risk of bias

The review of Klomp at al. did not provide the dates of databases searched nor the keywords used in searching. [56] It did not provide a list of excluded studies, nor the characteristics of included studies. The scientific quality of included studies was not used in formulating conclusions, publication bias was not assessed and conflicts of interest were not stated. The review by Ubbink and Vermeulen[57, 58] scored well on all items of the AMSTAR checklist, except that it did not assess publication bias (Table 28 in the appendix).

3.3.5.6. Effects of interventions

There was low quality evidence that SCS had no effect on mortality, compared to conservative medical management (RR: 0.92; CI: 0.64 to 1.34; n=5) (Klomp 2009). There was low quality evidence that SCS reduced amputation incidence in both reviews, with a slight difference in risk reduction estimates between reviews (Klomp: RD: -0.07; CI: -0.17 to 0.03; n=5 studies; Ubbink: RD: -0.09; CI: -0.19 to 0.01; n=5 studies).

In addition, there was low quality evidence that more patients on SCS reached Fontaine stage II (RD: 0.33; CI: 0.19 to 0.47; n=2 studies) and very low quality evidence that more patients on SCS reached Fontaine stage III (RD: 0.07; CI: -0.24 to 0.38; n=2 studies). This implies that for every three patients with critical limb ischemia treated with SCS, one patient would improve to claudication (NNT: 3; CI: 2 to 5). There was low quality evidence that SCS treatment did not improve quality of life (MD on the Nottingham health profile: 1; CI: -0.02 to 2.2; n=1 study) (Ubbink 2005-2009).

The overall risk of complications with SCS was 17% (CI: 12-22%), resulting in a number needed to harm of six (CI: 5-8). Re-intervention was required in 15% (CI: 10-20) of patients because of changes in stimulation, while 3% (CI: 0-6%) of patients had an infection of the lead or pulse generator (Ubbink 2005-2009) (Table 35 and Table 36).

3.3.5.7. Discussion

There are some differences between those two systematic reviews. The main outcome presented by Ubbink and Vermeulen was the amputation incidence meta-analysed across five RCTs plus one CT. Amputation incidence was significantly lower in SCS treated patients, compared to conservative treatment alone (RD: -0.11; CI: -0.20 to -0.02; 6 studies). In a sensitivity analysis that excluded the CT, the risk difference for amputation incidence decreased slightly and was no longer significant (RD:-0.09; CI:-0.19 to 0.01; 5 studies) (Ubbink 2005-2009[57, 58]).

The reason for the difference with the risk difference obtained by Klomp et al. [56] (RD: -0.07; CI:-0.17 to 0.03) using the same studies, might be that they used a random effects model, whereas Ubbink and Vermeulen used a fixed effects model. However, because there was no heterogeneity for this outcome (I^2=0.0%) the use of a fixed effect model might be justified. An additional reason might be that eleven patients with Buerger's disease were excluded from the meta-analysis by Ubbink and Vermeulen.

When we re-ran this meta-analysis in Comprehensive Meta-Analysis using amputation events provided by Klomp et al. (which were identical to those provided by Ubbink and Vermeulen except for the 11 excluded patients) and applying a fixed effects model, we obtained a risk difference for amputation and CI identical to the risk difference reported by Klomp et al.

Although the differences between the sheer numbers are small and on the border of significance, the authors draw different conclusions. Ubbink and Vermeulen conclude that ´there is evidence to favour SCS over standard conservative treatment alone to improve limb salvage and clinical situations in patients with non-reconstructable limb ischemia´. In contrast, Klomp et al. conclude that ´meta-analysis including all randomised data shows insufficient evidence for higher efficacy of SCS treatment compared with best medical treatment alone´.

3.3.5.8. Conclusion

There was low quality evidence that SCS reduced amputation rates in patients with critical, inoperable limb ischemia. One in six patients needed a re-intervention or experienced an infection.

3.3.6. Spinal cord stimulation in patients with refractory angina pectoris (RAP)

Five RCTs described the effectiveness of SCS in patients with refractory angina (De Jongste 1993,[53] ESBY 1998,[90-93] Hautvast 1998,[54] Lanza 2011,[83] and McNab 2006[94]).

3.3.6.1. Sample sizes and setting

Sample sizes were relatively small, with the largest trial including 104 participants (ESBY 1998) and three trials including 25 or fewer participants.

Four trials were single centre trials (two from the Netherlands, one from Sweden (two centres) and one from the United Kingdom) and one Italian trial was a multicentre study (Table 29).

3.3.6.2. Participants

Participants in all trials were diagnosed with refractory angina. Participants from four trials were not eligible for coronary artery bypass grafting (CABG) or conventional percutaneous coronary interventions. The participants in the fifth trial would have no prognostic benefit from CABG (only symptomatic indication) or had a high risk of surgical complications with no possibility for conventional percutaneous coronary intervention (ESBY 1998) (Table 29).

3.3.6.3. Interventions

One trial compared SCS versus no SCS (De Jongste 1993); two trials compared SCS versus sham SCS (Hautvast 1998 and Lanza 2011); one trial compared SCS versus CABG (ESBY 1998); and one trial compared SCS versus percutaneous myocardial laser revascularisation (McNab 2006) (Table 29).

3.3.6.4. Outcomes

Reported outcomes were mortality, angina-related outcomes (nitrate intake, anginal attack frequency, exercise time), pain scores (visual analogue scale (VAS) and linear analogue self assessment scale (LASA)), Canadian Cardiology Class, self estimated treatment effect, activities of daily living and disease specific quality of life score (Seattle Angina Questionnaire (SAQ)), and adverse effects (Table 29). With a few exceptions the reported outcomes were short term (a few weeks to a year).

3.3.6.5. Risk of bias

Four out of five trials had an unclear risk of bias for the random sequence generation and allocation concealment; the fifth trial (McNab 2006) had a low risk of bias in these domains (Table 27). The risk of bias through the way the blinding of participants or personnel was handled was assessed to be ´high´, except in one trial were the risk was assessed as ´low´ (Hautvast 1998). The risk of detection bias was assessed to be ´high´ for three trials (De Jongste 1993; ESBY 1998; McNab 2006). One trial was assessed as having a ´high´ risk for attrition bias, because of the amount of incomplete outcome data (Lanza 2011). The risk of reporting bias, through selective reporting of outcomes, was assessed as ´low´ for all five trials. Two trials were (in part) industry sponsored which was assessed as a ´high´ risk of bias (Lanza 2011; McNab 2006). Two studies were not industry sponsored (ESBY 1998; Hautvast 1998) and for one trial the source of funding was unclear (De Jongste 1993) (Table 27).

3.3.6.6. Effects of interventions

In the one study that compared SCS versus no SCS (De Jongste 1993) there was low quality evidence that SCS was more effective in reducing nitrate intake and anginal attacks, and in improving activities of daily living (ADL) score, but not in prolonging exercise time or time to angina at two months. The mean nitrate intake/week for the SCS group was 1.7 (SD: 1.7) vs 12.0 (SD: 4.0) ($p<0.01$) in the no-SCS group; mean angina attacks/week: 6.3 (SD 5.1) vs 16.3 (7.9) ($p=0.01$) respectively; mean total exercise time: 10.8 minutes (SD: 4.1) vs 10.8 (SD: 4.0) ($p=1$); mean time to angina: 10.9 minutes (SD: 3.9) vs 10.4 (SD: 4.0) ($p=0.77$) (p-values for between-group differences calculated by us). Adverse effects were not reported on.

The two studies that compared active SCS versus sham (= not active) SCS (Hautvast 1998 and Lanza 2011) gave conflicting evidence of very low quality on the effectiveness of SCS in diminishing nitrate intake, anginal attacks or pain on a visual analogue scale. One trial reported no difference between SCS and sham SCS at six weeks (Hautvast 1998) and the other trial reported an improvement with SCS at 1 month (Lanza 2011).

In addition, there was moderate quality evidence that SCS is not more effective than sham SCS in prolonging exercise time (10.8 (SD: 4.1) vs 10.8 m (SD: 4.0) minutes; p=1.0), time to angina (10.9 (SD: 3.9) vs 10.4 (SD: 4.0) minutes; p=0.77) or improving VAS or LASA pain scores at 6 weeks (p-values for between-group differences calculated by us) (Hautvast 1998). There was low quality evidence that the mean Canadian Cardiology Class was better in SCS treated patients versus sham SCS treated patients (2.10 (SD: 1.1) vs 3.25 (SD: 0.9) (p=0.01), and that there was an improvement with SCS on two out of five domains of the Seattle Angina Questionnaire (all at 1 month) (Lanza 2011). Hautvast et al. reported that there were no adverse events while; Lanza et al. did not report on adverse events.

The largest study compared SCS versus CABG and provided low quality evidence that mortality was lower in SCS treated patients at six months (1 vs 7; p=0.02) but not at 2 years (5 vs 10; p-value not reported) (ESBY 1998). Cerebrovascular morbidity was higher in the CABG group at six months (2 vs 8, p=0.03). Non-fatal or total morbidity (the sum of mortality and non-fatal morbidity) at six months did not differ between groups. There was low quality evidence that there was no difference in nitrate intake (4.1 (SD: 10.5) vs 3.1 (SD: 8.7); p-value not reported), anginal attacks (4.4 (SD: 7.4) vs 5.2 (SD: 10.3); p-value not reported) or a self-reported treatment effect (83.7% vs 79.5%; p-value not reported) at six months. Three patients had their spinal cord electrodes surgically corrected. The stimulator had to be removed because of infection in one patient but no additional infections occurred in the SCS group. The average life span of the SCS pulse generators before replacement was 3.6 years.

The one study that compared SCS versus percutaneous myocardial laser revascularisation (McNab 2006), provided low quality evidence for no difference between treatments at 12 and 24 months in exercise time, time to angina or no angina during exercise. Adverse events were more frequent in the SCS group at 12 months (57 vs 26, p<0.01) but not at 24 months (69 vs 59, ns). Excess adverse events at 12 months were SCS related. Severe adverse events (events requiring admission, prolonged stay in hospital or surgery, or that were life threatening or ultimately resulted in death) were also more frequent in the SCS group at 12 months (41 vs 24, p<0.01), but again not at 24 months (62 vs 54, ns).

All effects and their corresponding GRADE assessments are given in Table 30.

3.3.6.7. Discussion

The trials that evaluated SCS in patients with refractory angina were relatively small to very small, and showed various problems. Most trials reported relative differences, whereas absolute differences would have been preferable. Two trials synthesised data from within-group differences (i.e. pre-post change), instead of between-group differences (De Jongste 1993[53]; Hautvast 1998[54]). To reliably assess the effectiveness of any treatment, it is necessary to evaluate its outcomes compared to a control group. Reporting of within group changes reduces the effect of randomisation to a ´before-after´ study design. And comparing the pre-post change of two randomised groups is not the conventional method of reporting randomised trial results. By recalculating some results from the original data, we found different results from those highlighted in the original studies. The authors of the Hautvast 1998 trial evaluated the differences between groups in pre-post changes, and found a significant difference in total exercise time, time to angina, nitrate consumption, anginal attacks and ischemic episodes, all in favour of SCS. We found no statistically significant differences between SCS and control group for these outcomes when we recalculated their data to post-treatment differences (Table 29).

Three trials reported on SCS versus no SCS or sham SCS. It seems that the comparisons of SCS versus sham SCS are more valid than the comparison of SCS versus no SCS because these might partly eliminate the placebo effect. Overall, the results from these three trials were conflicting. The trial with the lowest risk of bias found no significant between-group differences (Hautvast 1998). The between-group difference in time to angina was borderline significant (p=0.06). Even so, the difference between 319 vs 246 seconds is very small and its clinical significance seems very low. The follow-up for the SCS vs no SCS or sham SCS trials was short for a chronic condition (1 to 2 months). Adverse events were not systematically recorded in these trials.

The higher mortality and higher cerebrovascular morbidity after CABG, found in the ESBY study[90-93] are compatible with a reported high mortality

and cerebrovascular morbidity associated with CABG in this patient population.

3.3.6.8. Conclusion

There was moderate quality evidence that SCS was not more effective compared to sham SCS in improving total exercise time and time to angina. There was conflicting evidence of very low quality on the effectiveness of SCS compared to sham SCS in diminishing nitrate intake, anginal attacks or pain on a visual analogue scale. There was low quality evidence that the mean Canadian Cardiology Class was better in SCS treated patients versus sham SCS treated patients, and that there was an improvement with SCS on two out of five domains of the Seattle Angina Questionnaire. The long-term (over two months) effectiveness of SCS in comparison to sham SCS has not been evaluated.

There was low quality evidence, in a subgroup of patients with refractory angina whom had no prognostic benefit of CABG or whom had an increased surgical risk, that SCS was as effective as CABG at six months in lowering nitrate intake or anginal attacks. CABG-treated patients had a higher mortality and cerebrovascular morbidity at six months, but not at 2 years.

There was low quality evidence that SCS was equally effective compared to percutaneous myocardial laser revascularisation regarding exercise time, time to angina or no angina during exercise, with more severe adverse events at 12 months but not at 24 months.

No specific evidence comparing different devices, different electrode types or different stimulation patterns was identified in those RCTs.

3.3.7. Intrathecal Analgesic Delivery Pumps

One RCT evaluated the effectiveness of IADP (Smith 2002[95]).

3.3.7.1. Sample size and setting

Prospective, multicentre RCT sponsored by Medtronic including 200 cancer patients worldwide. All participating sites had pain management centres with a structured approach to pain management, where IADP was routinely used for the management of cancer pain.

3.3.7.2. Participants

Patients with advanced cancer and refractory pain, who had an average pain score on a visual analogue scale ≥ 50 mm despite 200 mg/day of oral morphine or equivalent. Morphine intake was allowed to be lower if there were opioid side effects refractory to treatment that prevented the upwards titration of morphine (Table 37 in the appendix).

3.3.7.3. Interventions

The interventions were IADP (starting with morphine) plus comprehensive medical management compared to comprehensive medical management alone (Table 37).

3.3.7.4. Outcomes

The outcomes assessed were: pain reduction ≥ 20% on a visual analogue scale; no pain reduction but ≥ 20% toxicity reduction; both toxicity and pain reduced ≥ 20%; neither pain nor toxicity reduced ≥ 20%; and adverse events (Table 37).

3.3.7.5. Risk of bias

The risk of bias through random sequence generation was unclear and the risk of bias through allocation concealment was assessed as ´low´. The trial was not blinded and the risk of bias through blinding of participants, personnel and outcome assessors, and through the handling or amount of incomplete data was assessed as ´high´. The risk of bias through selective reporting was assessed as 'low'. The trial was industry sponsored (Table 27).

3.3.7.6. *Effects of interventions*

There was low quality evidence that either pain or toxicity was reduced by IADP by at least 20% (84.5 vs 70.8%; p=0.05), and that both pain and toxicity were reduced by at least 20% (57.7% vs 37.5%; p=0.02). There was moderate quality evidence that fewer IADP patients had neither a pain nor a toxicity reduction of at least 20% (11.3% vs 23.6%; p=0.05). This study also reported a non-significant improved survival at six months (53.9% alive vs 37.2%, p= 0.06) There was low quality evidence that there was no difference in the frequency of serious adverse events since these occurred evenly in both groups (51% vs 49%). In eight cases pump revision or explantation was necessary (Table 37 and Table 38).

3.3.7.7. *Discussion*

This study has the benefit of providing RCT based evidence for the management of chronic refractory cancer pain with IADP. However, the results described are borderline significant. Moreover, the reporting is not always clear.

The authors did not clearly define refractory cancer pain and the need for 200 mg or more of oral morphine per day seems to be arbitrary and not an accepted definition of refractory cancer pain. There were two populations of patients in this study: those with side effects limiting dose escalation and those who reached the arbitrary 200 mg of oral morphine per day limit without opioid toxicity. These two subsets of patients are likely to be managed differently in usual clinical practice. Moreover, the median age of the patients (~ 57 years) seems rather low. Therefore, it is unclear whether this study truly represents the cancer population at risk.

In the reporting, the terms ´intrathecal´ and ´intraspinal´ were used interchangeably. The reporting of the serious adverse events is obscure and its statistical interpretation non-existent, although the overall frequency of adverse events is relatively high.

3.3.7.8. *Conclusion*

There was low quality evidence that IADP plus comprehensive medical management was more effective than comprehensive medical management alone in reducing pain and toxicity in cancer patients with refractory pain, and that there was no difference in the frequency of serious adverse events.

3.4. Ongoing clinical trials

The number and quality of interventional studies on neuromodulation techniques is disappointing. Therefore, we also tried to identify ongoing and planned interventional research by searching ClinicalTrials.gov.

For SCS a search on ‘Spinal Cord Stimulation OR SCS’ produced 190 hits in the database, but only 87 trials related to devices and 34 of those to SCS devices. The trials were in various states of recruitment and some were terminated without results available. The trials were most often on newer types of devices, head to head comparisons of different devices etc. The indications included mainly those indications discussed previously in this chapter, but also other indications such as diabetic neuropathy and heart failure.

A similar search for IADP (‘intrathecal drug OR IADP OR IDDD’) produced 241 hits but only 8 of these were about devices, including 5 on IADP. The remaining trials were mainly comparing different drugs, or concerned other intrathecal procedures.

3.5. Discussion

3.5.1. Evidence from interventional research

Two systematic reviews and nine randomised controlled trials provided the evidence from interventional research on the effectiveness of SCS or IADP in patients with chronic refractory pain. Risk of bias and/or small study sizes led to the downgrading of most outcomes by two levels to *´low quality evidence´*, and to the downgrading of a few outcomes by one level to *´moderate quality evidence´*.

There was low quality evidence that SCS was more effective than CMM in reducing pain in patients with failed back surgery syndrome or complex regional pain syndrome.

There was low quality evidence that SCS reduced the incidence of amputation in patients with critical limb ischemia.

There was moderate or low quality evidence that SCS was as effective as various medical treatments or sham SCS for patients with refractory angina, with conflicting evidence of low quality for some outcomes.

There was low quality evidence that IADP was more effective than comprehensive medical management alone in reducing pain and toxicity in cancer patients with refractory pain.

Although the available evidence on neuromodulation from interventional research is limited and mainly of low or very low quality, this needs to be put into perspective.

As can be seen from the GRADE assessments in the appendix, the available evidence, is classified as low quality evidence due to the strict criteria used and mainly because of:

- Methodological weaknesses in the study design mainly related to poor or absence of blinding
- Imprecision problems related to small study sizes
- Short time follow-up due to cross-over of patients
- Inherent limitations in the assessment of pain outcomes

Practical difficulties for getting information from RCTs only are not restricted to research on interventional pain management. But, recently new methods for the design of clinical trials in interventional pain research have been proposed, including other randomisation schemes, such as the pre-randomisation design.[96] However, those innovative schemes for asking informed consent only after randomisation and treatment, and to avoid *'medical shopping'* due to information given during the study, have received mixed evaluations from Institutional Review Boards ('ethical committees') in various countries.

These problems for conducting research, further illustrated by the paucity of ongoing clinical trials, indicate that no new strong evidence from RCTs should be expected in the near future.

In contrast with those disappointing results from interventional research, the literature abounds with more positive accounts from personal experience, case series and reviews that, overall, show a much more positive picture of the therapeutic efficacy of neuromodulation. Reviews and comments also offer further explanations for the absence of hard evidence from RCTs:

- Randomization is often considered unethical in those persons suffering from extreme chronic pain, when the treating physician is confident the proposed therapy is superior
- Sham therapy might therefore also be considered unethical
- Sham therapy is difficult to achieve and blinding is impossible, since both patient and physician are aware of the therapy (no real blinding possible)
- Neuromodulation is never a stand-alone intervention but is used in the context of a complete management of chronic pain conditions that are difficult to standardise

The most difficult problems in the evaluation of treatment efficacy in pain research are 1) what is a successful outcome and 2) how to measure it? It was recommended that six core outcome domains should be considered when designing chronic pain clinical trials: pain, physical functioning, emotional functioning, participant ratings of improvement and satisfaction with treatment, symptoms, and adverse events and participant disposition.[97] However, few studies in practice comply with these recommendations.

3.5.2. Safety issues

RCTs are not well suited to document adverse events. Apart from the previously mentioned and anecdotically reported incidents directly related to surgery or to the functioning of the system there are other documented safety issues, especially related to the intrathecal delivery of opioids. As mentioned in chapter 2 the intrathecal delivery of opioids has been reported to be associated with several drug related complications including general endocrine complications,[45] increased mortality rates,[46, 47] or the development of inflammatory mass lesions at the tip of the catheter.[48]

3.5.3. Evidence from observational research

There is clearly a lack of evidence from RCTs on efficacy. However, concerning effectiveness there are many narrative and non-systematic reviews of the observational evidence on neuromodulation in the scientific literature. The most serious effort to assess neuromodulation using an evidence based approach was made by an academic consortium of pain specialists. They recently assessed the evidence for several specific indications separately, summarizing the available evidence on interventional pain management, including evidence from observational research and weighing this against observed adverse events for several specific indications.

This research appeared as an evidence based medicine series in the scientific journal Pain Practice from 2009 until 2011,[11, 13, 15, 98] and was recently also published as a book.[99] In those publications the authors assess the evidence of specific interventional pain therapies for several conditions and weigh it against its observed adverse effects using the scheme developed by Guyatt et all. *'Grading strength for clinical guidelines'*.[100-102]

An overview of the recommendations, relevant for SCS and IADP per indication is given in Table 1. These evidence ratings and recommendations are given for reference and have not been double checked by the authors of this report.

The main conclusion of those assessments is that for several of these indications neuromodulation can have a role in the management of chronic pain, but that it is to be considered as a technology of last resort, after a proper patient work-up by a truly multidisciplinary team of pain specialists. The importance of proper patient selection is also highlighted.

Table 1 – Evidence ratings and recommendations for evidence on SCS or IADP from both interventional and observation research [99]

Recommendation	Intervention and indication
Positive recommendation	• SCS for FBSS (in specialised centres only) • SCS for CRPS (in specialised centres only) • SCS for refractory angina pectoris (in specialised centres only) • IADP for patients with cancer pain
Considered, preferably study related	• SCS for post-herpetic neuralgia • SCS for painful diabetic polyneuropathy • SCS for ischemic pain due to vascular disease • SCS for pain in chronic pancreatitis
Only study-related	• SCS for cervical radicular pain • SCS for meralgia paresthetica • SCS for phantom pain • SCS for traumatic plexus lesion

Positive recommendation: evidence ratings 1A+ to 2B+; considered, preferably study-related: 2B± and 2C+ ; only study-related: 0.

3.5.4. Conclusion

Neuromodulation can only be considered in selected patients after having completed a full assessment by a truly multidisciplinary team of pain specialists in an experienced and specialised pain centre. Its application in a specific patient should be preceded by a thorough and stepwise pain management approach where less invasive treatment options have failed. It is an interventional approach that is not risk-free and evidence about its efficacy is limited.

3.6. Key points

Neuromodulation should only be considered in selected patients afterother chronic pain management techniques have failed. It is an interventional approach that is not risk-free and evidence about its efficacy is limited.

No new strong evidence is expected in the foreseeable future because of the inherent problems associated with this research, illustrated by the few ongoing RCTs.

Therefore it should only be considered in patients with chronic refractory pain after a complete assessment and attempts to manage the condition with non-interventional methods by a truly multidisciplinary team of pain specialists in an experienced and specialised pain centre.

Evidence on effectiveness from RCTs is limited and of low quality. It shows:

- **In patients with failed back surgery syndrome:**
  - **There was low quality evidence that SCS was more effective than repeated lumbosacral spine surgery at three years in relieving pain;**
  - **There was low quality evidence that SCS was more effective than conventional medical management at six months in providing leg pain relief.**
- **In patients with complex regional pain syndrome:**
  - **There was low quality evidence that SCS plus physical therapy was more effective in reducing pain than physical therapy alone;**
  - **38% of patients with SCS had needed a re-intervention at two years.**
- **In patients with inoperable critical limb ischemia:**
  - **There was low quality evidence that SCS reduced amputation rates in patients with critical, inoperable limb ischemia;**
  - **One in six patients needed a re-intervention or experienced an infection.**
- **In patients with refractory angina pectoris:**
  - **There was moderate quality evidence that SCS was as effective as sham SCS in improving total exercise time and time to angina;**
  - **There was conflicting evidence of very low quality on the effectiveness of SCS compared to sham SCS in diminishing nitrate intake, anginal attacks or pain on a visual analogue scale;**
  - **There was low quality evidence that SCS was as effective as CABG at six months in lowering nitrate intake or anginal attacks. CABG-treated patients had a higher mortality and cerebrovascular morbidity at six months, but not at 2 years;**
  - **There was low quality evidence that SCS was equally effective compared to percutaneous myocardial laser revascularisation regarding exercise time, time to angina or no angina during exercise, with more severe adverse events at 12 months but not at 24 months.**
- **In cancer patients with refractory cancer pain:**
  - **There was low quality evidence that IADP plus comprehensive medical management was more effective than comprehensive medical management alone in reducing pain and toxicity;**
  - **There was low quality evidence that there was no difference in the frequency of serious adverse events.**

Based on additional observational evidence and using the Guyatt grading scheme other reviewers gave a positive recommendation for:

- **SCS for FBSS (in specialised centres only)**
- **SCS for CRPS (in specialised centres only)**
- **SCS for refractory angina pectoris (in specialised centres only)**
- **IADP for patients with cancer pain**

4. ECONOMIC EVALUATION

4.1. Introduction

This chapter provides an overview of studies evaluating spinal cord stimulation (SCS) or intrathecal analgesic delivery pumps (IADP) in the treatment of chronic, intractable pain from an economic perspective. The primary objective is to evaluate the potential cost-effectiveness of such techniques compared to other treatment alternatives.

4.2. Methods

4.2.1. Search strategy

A systematic search for relevant publications was carried out with the consultation of electronic reference databases up to the 18th of June 2012.

The Centre for Reviews and Dissemination (CRD) database, the Cochrane Database of Systematic Reviews (CDSR) and the websites of Health Technology Assessment (HTA) institutes listed on the INAHTA website (International Network of Agencies for Health Technology Assessment) were consulted to retrieve reviews of the economic literature on SCS or IADP.

Medline (through OVID), EMBASE and Econlit (through OVID) were searched to retrieve full economic evaluations (studies looking at competing alternatives from both a cost and an outcome perspective). An overview of the search strategy is given in the appendix.

4.2.2. Selection procedure

To select potentially relevant studies for inclusion in our review we first looked at the titles and abstracts before excluding any obvious studies that did not match our subject of interest. Articles that could have been relevant or for which we had doubts were retrieved and evaluated using their full text.

Relevant reviews and full economic evaluations were checked for additional references which could be of interest.

All studies finally included in this review were critically evaluated and a summary of their characteristics and results were extracted and presented in a table format in the appendix.

4.2.3. Selection criteria

Economic evaluations comparing SCS or IADP to any other available treatment alternative in patients suffering from chronic intractable pain were included in our review. Consultation of HTA websites to identify any relevant systematic reviews was done with the purpose of extending the potential list of relevant studies.

Prospective or retrospective case reviews with a very small sample size (less than 20 patients), or publications in the form of letters, editorials, notes, or abstracts only, as well as any cost descriptive studies not covering outcomes, were excluded from our review. Cost consequences studies, looking at costs and outcomes separately were included.

No further limitations were imposed.

An overview of the selection criteria used is given in Table 2.

4.3. Results

4.3.1. Overview of the search and selection process

After exclusion of duplicates our searches returned 500 unique citations. Of those references, 440 did not meet our inclusion criteria based on title and/or abstract alone.

Of the 60 citations left, 33 were excluded from the analysis after full-text assessment. Twelve reviews, three in IADP[74, 76, 103] and nine in SCS,[12, 60, 63, 69-71, 104-106] were explored for additional evaluations and a total of 16 economic analyses (only 2 in IADP and 14 in SCS) were considered relevant and included in our review.

The analysis of the articles' references and the HTA websites brought 2 additional citations, which were finally excluded from our analysis, resulting in 15 economic evaluations and one study including both an economic evaluation and a review of the literature, for inclusion in our review. Figure 16 in the appendix shows the flow chart of the literature selection process.

An overview of the selected studies is shown in Table 3 for studies on spinal cord stimulation and in Table 4 for intrathecal analgesic delivery pumps.

Table 2 – Selection criteria for economic evaluations

Selection Criteria	Inclusion Criteria	Exclusion Criteria
Population	Patients suffering from chronic refractory pain	Any other patient groups
Intervention	SCS or IADP	Any other therapies
Design	Systematic reviews or full economic evaluations (primary or secondary)	Cost descriptive analysis, cost comparisons
Type of publication	Articles or reviews	Letters, editorials, notes, conference review articles or abstracts
Sample size	Retrospective or prospective case reviews with N>20 patients and all RCTs	Retrospective or prospective case reviews with N≤20 patients

Table 3 – Overview of economic evaluations of spinal cord stimulation

Author	Year	Country	Sample size	Type of analysis	Perspective	Time horizon (in years)	Discount rate (%)
Hollingworth[107]	2011	USA	158	Cost-effectiveness	Third party payer	2	3 (costs)
Kemler[108]	2010	UK	Model	Cost-utility	Health services	15	3,5
Taylor[109]	2010	UK	Model	Cost-utility	Health services	15	3,5
Simpson[12]	2009	UK	Model	Cost-utility	Health services	15	3,5
Dyer[110]	2008	UK	68	Cost-utility	National health insurance	2	3,5
Manca[40]	2008	Europe, Canada, Australia, Israel	100	Cost-effectiveness	Health services	0,5	Not necessary since time horizon less than 1yr
North[111]	2007	USA	42	Cost-effectiveness+ cost-utility	Hospital health services	3,1	NA
Klomp[112]	2006	Netherlands	120	Cost-consequences	Societal	2	NA
Taylor[113]	2005	UK	Model	Cost-utility	Health services	2+ lifetime	6(costs),1,5%(outcomes)
Blond[114]	2004	France	43	Cost-consequences	Health services	2	NA
Yu[115]	2004	Sweden	24	Cost-consequences	Health services	4,5 (3 prior implant and 1,5 post)	NA
Andrell[92]	2003	Sweden	104	Cost-consequences	Health services	2	NA
Kemler[87]	2002	Netherlands	54	Cost-effectiveness+ cost-utility	Societal	1 + lifetime	3
Kumar[116]	2002	Canada	104	Cost-consequences	Health services	5	NA

Table 4 – Overview of economic evaluations of intrathecal analgesic delivery pumps

Author	Year	Country	Sample size	Type of analysis	Perspective	Time horizon (in years)	Discount rate (in %)
Kumar[117]	2002	Canada	67	Cost- consequences	Health services	5	NA
De Lissovoy[118]	1997	USA	Model	Cost-effectiveness	Third party payer	5	5(costs)

4.3.2. Study design

As shown in Table 3 and Table 4, the majority of the studies included in our review were performed in Europe: five in the UK,[12, 108-110, 113] two in the Netherlands, [87, 112] two in Sweden,[92, 115] and one in France.[114] Three studies were carried out in the USA,[107, 111, 118] and two in Canada.[116, 117] Finally, one study was a multicentre study involving 12 different sites in Europe, Canada, Australia, and Israel.[40]

4.3.2.1. Spinal Cord Stimulation

All of the 14 economic evaluations included in this review on SCS for the treatment of chronic intractable pain were published after 2001. Among these, six were economic evaluations undertaken alongside randomised trials,[40, 87, 92, 110-112] while four were observational studies looking at case series,[107, 114-116] one of them retrospectively.[115]

The remaining four studies were designed as decision analytic models and Markov models.[12, 108, 109, 113]

4.3.2.2. Intrathecal analgesic delivery pumps

From the two studies included for IADP, one dated from 2002[116] and consisted of a trial-based economic evaluation, while the other, published in 1997, [118] consisted of a simulation model based on published literature.

4.3.3. Type of economic evaluation

4.3.3.1. Spinal cord stimulation

Four of the 14 studies included in this review were cost-utility analyses evaluating both the costs and the impact of SCS on patients' Health Related Quality of Life (HRQoL).[108-110, 113] There were two cost-effectiveness studies combining measures of effectiveness with costs,[40, 107]. Only three studies analysed their results both from cost-effectiveness and a cost-utility perspective.[31, 87, 111] The remaining five studies consisted of cost-consequences analyses in which the authors analysed both costs and outcomes but did not attempt to present them in a combined manner.[112 92, 114-116]

The main outcome taken into consideration in the studies varied depending on the indication in which the study focused. All studies on failed back surgery syndrome (FBSS),[12, 40, 107, 109, 111, 113, 114, 116] critical limb ischemia (CLI),[112] and complex regional pain syndrome (CPRS),[12, 87, 108] looked at changes in pain and/or QoL. The studies focusing on angina pectoris (AP) presented a more diverse choice of outcomes.[92, 110, 115]). We will discuss this in more detail in section 4.3.8.

4.3.3.2. Intrathecal analgesic delivery pumps

The study by De Lissovoy et al on IADP consisted of a cost-effectiveness analysis looking at pain relief as the main outcome.[118]. The study by Kumar et al,[117] a cost-consequences analysis, studied both HRQoL and patient satisfaction.

4.3.4. Time frame of analysis

The timeframe of the studies varied greatly from a low of six months,[40] to a high of a life time.[87, 113] As many as eight studies presented a timeframe of less than five years and did not attempt to extrapolate their results over a longer time period.[40, 92, 107, 110-112, 114, 115] The studies on IADP both presented a timeframe of five years.

For the devices covered in this review a timeframe of less than five years may be too short to capture overall costs for two main reasons: first, these are devices that can initially be expensive whereas their benefits could accumulate over time and second, most are battery operated and may require replacements after a relatively short time period. The latter is particularly important for SCS while it is not so for IADP where battery operated pumps seem to have longer lives. The length of the IPG battery life in SCS will be discussed in more detail in chapters 3 and 8 of this report, but given its potential importance, we have also included its impact later on in this chapter.

4.3.5. Discounting

Only eight of the 15 papers which used a time horizon of over a year applied discounting. Four of the five UK studies applied a rate of 3.5% to both costs and outcomes,[12, 108-110] while the remaining applied a 6% rate for costs and a 1.5% for outcomes.[113] Two more studies, one Dutch[87] and one American study[107] applied a 3% discount rate although the former used it only for costs. One of the studies on IADP applied a 5% rate,[118] for costs.

4.3.6. Perspective

All but three studies,[87, 107, 112] limited their analysis to medical or hospital costs and only one of the former included indirect costs in their analysis.[112] Two of these three studies offering a wider perspective,[87, 112] did attempt to cover patient out of pocket expenses, while Hollingworth et al [107] tried to capture the cost of productivity losses.

4.3.7. Population size

Overall, the sample size of the studies included in our review was low, ranging from a high of 158 patients,[107] to a low of 24 patients.[115] From the 11 population-based studies only four included more than 100 patients,[92, 107, 112, 116] all of which focused on SCS. The only population based study on IADP included in our review had a sample size of 67 patients.[117]

4.3.8. Indications and comparators

4.3.8.1. Spinal cord stimulation

Eight out of the 14 studies on SCS focused on failed back surgery syndrome (FBSS), [12, 40, 107, 109, 111, 113, 114, 116] while three analysed the impact of SCS on complex regional pain syndrome (CRPS),[12, 87, 108] and a further one studied SCS on critical limb ischemia.[112] Finally, three studies focused on refractory angina pectoris.[92, 110, 115] The comparators used in these last three studies differed, as expected, from those used for other indications.

FBSS

Although the comparator used in FBSS studies was often described as conventional medical management (CMM), which covered both pharmaceutical and non-pharmaceutical therapies including re-intervention, the specific definitions differed slightly. Three studies compared SCS with re-intervention,[12, 109, 111]) and one compared SCS, not just to usual care, but also to treatment in a specialised pain clinic.[107] The study by Blond et al.[114] consisted of a before and after implantation comparison.

CRPS

From the three evaluations covering CPRS, the two most recent compared the combination of SCS and CMM with CMM alone,[12, 108] while the remaining explored the combination of SCS and physical therapy versus physical therapy alone.[87]

CLI

Only one study on critical limb ischemia was found, which compared SCS in combination with standard treatment against standard treatment alone (i.e. analgesics, antithrombotic and haemorrheologic drugs, local wound care and, only when indicated, antibiotics).[112]

RAP

The studies in refractory angina pectoris presented more variation regarding the choice of comparator. Andrell et al.[92] compared SCS with coronary artery bypass grafting (CABG), while Dyer et al.[110] studied the impact of percutaneous myocardial revascularization (PMR). Yu et al [115] limited their study to a before and after cost-consequences comparison.

4.3.8.2. Intrathecal analgesic delivery pumps

The two only studies on IADP included in our review focused on FBSS, and both looked at the impact of IADP therapy versus that of alternative conventional pain management, which included, in both cases, medical and non-medical therapies.[117, 118]

Table 5 – Costs of spinal cord stimulation and intrathecal analgesic delivery pumps

SPINAL CORD STIMULATION Study	Country	Original currency	Costing year	Time horizon (years)	Intervention	(Medical) cost/patient/ month in € (year 2011)
FAILED BACK SURGERY SYNDROME (FBSS)						
Hollingworth 2011	USA	US$	2007	2	SCS	1888
					Pain clinic	1261
					Usual care	869
Taylor 2010	UK	GBP	2010	15 (model)	SCS	654
					CMM	603
					SCS	654
					Re-operation	608
Simpson 2009	UK	GBP	2007	15 (model)	SCS+CMM	711
					CMM	630
					SCS+CMM	705
					Re-operation	629
Manca 2008	Europe, Australia, Canada, Israel	GBP	2006	0,5	SCS+CMM	3722
					CMM	882
North 2007	US	$	1995	3,1	SCS	1003
					Re-operation	1214
Taylor 2005	UK	€	2003	2	SCS	790
					CMM	644
Blond 2004	France	€	2003	2	Care prior to SCS implantation	257
					SCS	92
Kumar 2002	Canada	CAN$	2000	5	SCS	493
					Patients referred for SCS but not implanted	643
COMPLEX REGIONAL PAIN SYNDROME (CRPS)						
Kemler 2010	UK	GBP	2008	15 (model)	SCS+CMM	673
					CMM	619
Simpson 2009	UK	GBP	2007	15 (model)	SCS+CMM	694
					CMM	623
Kemler 2002	Netherlands	€	1998	1	SCS+PT	1068
					PT	625

SPINAL CORD STIMULATION						
Study	Country	Original currency	Costing year	Time horizon (years)	Intervention	(Medical) cost/patient/ month in € (year 2011)
REFRACTORY ANGINA PECTORIS (RAP)						
Dyer 2008	UK	GBP	2006	2	SCS	1094
					PMR	754
Yu 2004	Sweden	€	2001	4,5 (3 before +1,5 after)	SCS	991
					Cardiac care prior to SCS implantation	698
Andrell 2000	Sweden	€	2000	2	SCS	816
					CABG	936
CRITICAL LIMB ISCHAEMIA (CLI)						
Klomp 2006	Netherlands	€	1993	2	SCS+ Best medical treatment	2154
					Best medical treatment	1700
INTRATHECAL ANALGESIC DELIVERY PUMPS						
Study	Country	Original currency	Costing year	Time horizon (years)	Intervention	(Medical) cost/patient/
FAILED BACK SURGERY SYNDROME (FBSS)						
Kumar 2002	Canada	CAN$	2000	5	IADP	497
					CPT	643
DeLissovoy 1997	USA	US$	1996	5	IADP	1588
					Alternative medical management	1632

Table 6 – Outcomes for spinal cord stimulation and intrathecal analgesic delivery pumps

SPINAL CORD STIMULATION Study	Country	Time horizon (years)	Outcomes	Intervention	Outcome results	Reported p values
FAILED BACK SURGERY SYNDROME (FBSS)						
Hollingworth 2011	USA	2	Mean % of patients achieving: ≥50% leg pain reduction, less than daily opioid use and ≥2-point RDQ improvement at 24 months	SCS Pain clinic Usual care	5 3 10	p>0,05
Taylor 2010	UK	15 (model)	QALY/patient	SCS CMM SCS Re-operation	5,31 4,06 5,13 4,15	NA
Simpson 2009	UK	15 (model)	QALY/patient	SCS+CMM CMM SCS+CMM Re-operation	5,3 4,05 6,94 5,6	NA
Manca 2008	Europe, Australia, Canada, Israel	0,5	Mean improvements in EQ-5D scores from baseline at 6 months	SCS+CMM CMM	0,34 0,07	p<0,001
North 2007	USA	3,1	QALY/patient	SCS Re-operation	2,14 2,1	p=0,660
Taylor 2005	UK	2	QALY/patient	SCS CMM	0,67 0,604	NA
Blond 2004	France	2	Score - global pain -VAS (from 0-10) Owestry Disability Questionnaire score (over 100)	Care prior to SCS implantation SCS Care prior to SCS implantation SCS	7,99 3,9 54,8 33,3	p<0,01 p<0,01
Kumar 2002	Canada	5	Improvements in QoL (Owestry Disability Questionnaire)	SCS Patients referred for SCS, not implanted	27% 12%	NA
COMPLEX REGIONAL PAIN SYNDROME (CRPS)						
Kemler 2010	UK	15 (model)	QALY/patient	SCS+CMM CMM	4,84 2,88	NA
Simpson 2009	UK	15 (model)	QALY/patient	SCS+CMM CMM	7,71 7,36	NA
Kemler 2002	Netherlands	1	Mean improvement in EQ-5D scores from baseline Mean changes in pain intensity from baseline on a VAS scale (from 0 to 10) QALY/patient	SCS +PT PT SCS +PT PT SCS +PT PT	0,22 0,03 -2,7 0,4 NA	p=0,004 p<0,001

SPINAL CORD STIMULATION						
Study	**Country**	**Time horizon (years)**	**Outcomes**	**Intervention**	**Outcome results**	**Reported p values**
REFRACTORY ANGINA PECTORIS						
Dyer 2008	UK	2	QALY/patient	SCS	1,19	p>0,1
				PMR	1,07	
Yu 2004	Sweden	4,5 (3 before +1,5 after)	Median angina frequency/week	SCS	2,3	p<0,01
				Cardiac care prior to SCS implantation	14	
			Median Canadian Cardiovascular Society angina class	SCS	2	p<0,001
				Cardiac care prior to SCS implantation	3	
			Median weekly dose of nitroglycerin	SCS	1,5	p<0,01
				Cardiac care prior to SCS implantation	27,5	
Andrell 2000	Sweden	2	Number of patients with fatal or non-fatal myocardial infarctions; and mortality from heart or cerebrovascular disease	SCS	No stat. sig. difference	p>0,05
				CABG	No stat. sig. difference	
CRITICAL LIMB ISCHAEMIA						
Klomp 2006	Netherlands	2	Patient survival	SCS+Best medical treatment	64%	p=0,96
				Best medical treatment	63%	
			Limb survival	SCS+Best medical treatment	52%	p=0,47
				Best medical treatment	46%	

INTRATHECAL ANALGESIC DRUG PUMPS						
Study	**Country**	**Time horizon (years)**	**Outcomes**	**Intervention**	**Outcome results**	**P value**
FAILED BACK SURGERY SYNDROME (FBSS)						
Kumar 2002	Canada	5	Mean improvement in disability over study period (Oswestry Disability Index)	IADP	27%	NA
				CPT	12%	
De Lissovoy 1997	USA	5	Months free of pain	IADP	43,8	NA (values for IADP taken directly from lit,
				Alternative medical management	0	for alternative med. manag. assumed to be 0)

Table 7 – Reported ICERs for spinal cord stimulation and intrathecal drug delivery pumps

SPINAL CORD STIMULATION						
Study	**Country**	**Time horizon (years)**	**Outcome**	**Intervention**	**Reported incremental cost-effectiveness ratios**	**Probability of cost-effectiveness**
FAILED BACK SURGERY SYNDROME (FBSS)						
Hollingworth 2011	USA	2	Mean % of patients achieving: ≥50% leg pain reduction, less than daily opioid use and ≥2-point RDQ improvement at 24 months	SCS vs pain clinic	US$131 146	Very low (<5%) @ any threshold
				SCS vs usual care	US$334 704	
Taylor 2010	UK	15 (model)	QALY/patient	SCS vs CMM	GBP5 624	89% @ GBP20 000
				SCS vs re-operation	GBP6 392	82% @ GBP20 000
Simpson 2009	UK	15 (model)	QALY/patient	SCS+CMM vs CMM	GBP7 996	99% @ GBP20 000
				SCS+CMM vs re-operation	GBP7 043	100% @ GBP20 000
Manca 2008	Europe, Australia, Canada, Israel	0,5	HRQoL	SCS+CMM vs CMM	NA	NA
North 2007	USA	3,1	QALY/patient	SCS vs re-operation	SCS dominant	72% @US$40 000
Taylor 2005	UK	2/lifetime	QALY/patient	SCS vs CMM	over 2 years: €45 819/over lifetime: SCS dominant	Dominant (over a life time)
Blond 2004	France	2	Score global pain on VAS and Owestry Disability Questionnaire score	SCS vs medical treatment prior to SCS implantation	NA	NA
Kumar 2002	Canada	5	Improvements in QoL (Owestry Disability Questionnaire)	SCS vs alternative medical management	NA	NA
COMPLEX REGIONAL PAIN SYNDROME (CRPS)						
Kemler 2010	UK	15 (model)	QALY/patient	SCS+CMM vs CMM alone	GBP3 562	74%@GBP20 000
Simpson 2009	UK	15 (model)	QALY/patient	SCS+CMM vs CMM alone	GBP25 095	78% @GBP20 000
Kemler 2002	Netherlands	1/lifetime	QALY/patient	SCS+PT vs PT alone	over 1 year: €22 582/over lifetime: SCS dominant	Dominant (over a life time)
REFRACTORY ANGINA PECTORIS (RAP)						
Dyer 2008	UK	2	QALY/patient	SCS vs PMR	GBP46 000	30%@GBP30 000
Yu 2004	Sweden	4,5 (3 before +1,5 after)	Median angina frequency/week and Canadian Cardiovascular Society angina class	SCS vs cardiac care prior to SCS implantation	NA	NA
Andrell 2004	Sweden	2	Number of patients with fatal or non-fatal myocardial infarctions; and mortality from heart or cerebrovascular disease	SCS vs CABG	NA	NA
CRITICAL LIMB ISCHAEMIA (CLI)						
Klomp 2006	Netherlands	2	Limb survival	SCS+best medical treatment vs best medica treatment	€100 000	NA
INTRATHECAL ANALGESIC DRUG PUMPS						
Study	**Country**	**Time horizon (years)**	**Outcome**	**Intervention**	**Reported incremental cost-effectiveness ratios**	**Probability of cost-effectiveness**
FAILED BACK SURGERY SYNDROME (FBSS)						
Kumar 2002	Canada	5	Improvement in QoL (Oswestry Disability Index)	IADP vs CPT	NA	NA
DeLissovoy 1997	USA	5	Months free of pain	IADP vs alternative medical managment	IADP Dominant	Dominant

4.3.9. Overview of costs and outcomes

Table 5 shows the overall medical costs presented in the studies included in this review, per indication. Mean monthly costs over the entire study period are presented to facilitate comparisons across the different studies. Original costs have been standardised to € of 2011 by using consumer price indexes quoted by the OECD (www.oecd.org) and currency exchange rates as per August the 22nd 2012 (1 CND = 0.8076 EUR; 1GBP = 1.2668 EUR; 1 USD = 0.8018EUR). If the year of costing was not mentioned in the study the assumption was that quoted costs referred to one year before the publication date. For those studies in which costs were studied over more than one time horizon, we display the costs reported for the shortest time frame (more conservative approach).

4.3.9.1. Spinal cord stimulation

Leaving aside the study by Blond et al.[114] which did not include hospitalisation or implantation costs and thus was not comparable to the remaining published studies, overall monthly medical costs (in € of 2011) for SCS ranged widely from a high of € 3722 per month over a 6-months period[40] to a low of € 493 over a 5-year period.[116] These large cost differences appear to be, to some extent, affected by the overall time horizon of the study, with studies performed over longer time periods displaying lower cost differences or lower costs for SCS when compared to the alternative treatment. The weight of the time horizon is likely to be a direct consequence of the high costs of the initial procedure required for implantation, which is performed during the first months, after which the maintenance costs for SCS therapy diminish.

Thus, the two recent studies in FBSS, which stand out for reporting SCS costs of more than double when compared to usual care alternatives [40, 107] have a time horizon of two years or less, and while implantation costs appear to account for approximately 41% of the overall SCS costs in the study by Hollingworth et al., these go up to as much as 88% when looking at the study by Manca et al., performed over a 6-month period.

Of the 11 remaining studies, three showed lower costs of SCS when compared to the treatment alternative,[92, 111, 116] although the differences in costs found by North et al did not reach statistical significance.[111]

Two further studies[87, 113] which looked at a limited timeframe and then extended their calculations to patients' lifetime quoted the costs of SCS to be lower than those of the comparators by € 46 967 (2003 prices)[113] and € 58 471 (1998 prices),[87] only after extrapolation, highlighting, once more, the importance of the overall time frame.

The remaining six studies showed higher costs for SCS versus the alternative, but while cost differences appeared to be relatively small in those studies undertaken on FBSS or CRPS, ranging from € 46[109] to € 81[12] (in 2011 prices), the differences went up when looking at studies on RAP (from € 293 to € 340),[110, 115] and even more so when looking at CLI (€ 454).[112]

Table 6 shows an overview of study outcomes. If a study reported QALYs per patient in addition to other outcomes, only the former are displayed on the tables, because of their relevance from an economic perspective. Similarly to what we did for the costs, for studies that performed their analysis over more than one time horizon, we only display the outcomes reported for the shortest time frame (more conservative approach).

Only one of the eight studies in FBSS found negative results for SCS when compared with usual care,[107] but their results were not statistically significant. From the three studies in refractory angina, one did not find differences in the number of patients with fatal or non-fatal myocardial infarctions or the overall mortality from heart or cerebrovascular disease.[92] Similarly, the only study performed for SCS in critical limb ischemia, which focused on patient and limb survival, reported no differences between the SCS and the standard treatment groups.[112] The remaining studies showed positive outcomes for SCS versus the chosen comparator, with four reporting statistical significant differences: two in FBSS,[40, 114] one in CRPS[87] and one in RAP.[115]

Overall, seven studies captured quality adjusted life years (QALY) as their main outcome, and all of them favoured SCS over the comparator. The most commonly used instrument to draw utility scores was the EQ-5D questionnaire, a well validated and simple instrument providing descriptive profiles and a single index value for health status (www.euroqol.org).

For FBSS, two recent studies,[12, 109] used EQ-5D-based utility scores reported in the PROCESS trial specifically for this indication.[40] While a less recent study published in 2005 used utility values from the literature (not FBSS specific) and inputted them using a method adapted from Malter et al.[119] These same values were adopted by North et al in their research.[111]

For CRPS, Kemler et al used in their two studies[87, 108] responses collected via the EQ-5D during a clinical trial on CPRS patients[86] and applied UK specific population weights.[120] Simpson et al[12] on the other hand, adopted utility scores from a cross-sectional survey published in 2006, aimed at investigating neuropathic pain in 602 adults from six European countries.

For RAP, Dyer et al, also used UK weights for the utilities captured by means of the EQ-5D instrument at different times during their trial.[110]

In patients with FBSS, gains in terms of QALYs when SCS in combination with conventional care was compared to conventional care alone varied from a low of 0.066 QALY per patient over a 2-year time frame (1.12 QALY per patient over a patient's lifetime)[113] to 1.25 QALY per patient over a 15-year timeframe.[12, 109] When comparing SCS to re-operation in this same indication, gains ranged from 0.04 QALY per patient over 3,1 years[111] to 1.34 QALY per patient over 15 years.[12]

In CRPS, gains ranged between 0.35 and 1.96 QALY per patient over a 15-year period[12, 108] when SCS in combination with conventional care was compared with conventional care alone, and were of 0.18 QALY per patient over a 1-year time frame (2.33 QALY over a patient's lifetime) when SCS in combination with PT was compared to PT alone.[87]

Differences were small and not significant when SCS was compared to PMR (0.12 QALY per patient, $p>0.1$)[110] in patients suffering from RAP. Although these results were going in the same direction some did not provide p values while others did not reach statistical significant results for their outcomes[110, 111] and thus, the need for a sensitivity test was crucial.

Table 6 looks at the overall results in terms of cost-effectiveness ratios.

In FBSS, SCS appears to have both better outcomes and cost less than other medical alternatives (i.e. re-operation or usual care) according to 2 of the 4 studies reporting ICERs in that specific indication,[111, 113] and while North et al reported a probability of 72% for SCS to be cost-effective at a threshold of US$ 40 000, Taylor et al showed SCS to be dominant over a patient's lifetime for all sensitivity tests performed. Two recent studies[12, 109] did report low ICERs for SCS over a 15-year period versus both usual care (GBP 5624 and GBP 7996 reported by Taylor et al and Simpson et al respectively) and re-operation (GBP 6392 and GBP 7043 from Taylor et al and Simpson et al respectively) presenting SCS as an attractive treatment alternative, highly likely to be cost-effective at a threshold of GBP 20 000 (probabilities from 89% to 99% for SCS versus CMM and from 82% to 100% for SCS versus re-operation).

On the contrary, the observational study by Hollingworth et al [107] reported high ICERs, particularly when comparing SCS to usual care (US$ 334 704; 95%CI: US$ 142 203-US$ 489 243). Although this particular study was performed in a very specific patient population (workers' compensation recipients), presented a relatively low sample size (150 patients; 51 on SCS; 39 treated in a pain clinic and 68 on usual care) and was and observational study, it remains unclear why it shows such striking differences when compared to other published literature.

The three studies that looked at CRPS appear to show positive results when using SCS in combination with "usual care" or physical therapy, as opposed to "usual care" or physical therapy alone. While the least positive study[12] reported an ICER of GBP 25 095 over 15 years when comparing SCS to CMM, a further study[108] covering the same time horizon and comparing SCS to the same treatment alternative quoted a low ICER of GBP 3562. The remaining study[87] found that SCS was both cheaper and generated better outcomes (in terms of QALY per patient) than physical therapy alone, over a patient's lifetime. These results proved to be robust to the sensitivity analyses performed in all three studies.

Only one of the three studies on RAP displayed ICERs (GBP 46 000 per QALY) and quoted a small probability (30%) for SCS to be cost-effective against PMR, over two years, at a threshold of GBP 30 000.[110]

The only study found in CLI [112] found no differences in patient or limb survival in this population, while SCS was more expensive than usual care. No sensitivity analysis was performed.

4.3.9.2. *Intrathecal analgesic delivery pumps*

When looking at the cost of IADP, the two studies undertaken[117, 118] showed lower costs for IADP when compared to conventional care over a 5-year timeframe, with Kumar et al reporting statistically significant differences.[117] This same study also showed an improvement in QoL measured by means of the Oswestry Disability Index (27% with IADP versus 12% with conventional treatment over the study period). No p values were reported. For their modelling exercise De Lissovoy et al. used efficacy data from the literature and calculated a mean good-to-excellent pain relief of 73% for IADP which then used to estimate months free of pain for the IADP group (43.8 over a 60-month period). For the conventional treatment arm they assumed 0 months free of pain.

In terms of the overall results, only the study by De Lissovoy et al[118] displayed ICERs which showed that IADP was both cheaper and more effective (measured in terms of months of pain relief) than usual care although, as highlighted before, the model did present some strong assumptions linked to the efficacy of IADP versus that of conventional treatment and thus, its results should be interpreted with some caution.

More details on the main results of the individual studies can be found in the appendix.

4.3.10. Sensitivity analysis

4.3.10.1. *Spinal cord stimulation*

Six out of the 14 studies on SCS performed a probabilistic sensitivity analysis.[12, 107-109, 111, 113] Most of them presented their results on cost-effectiveness acceptability curves.

Best and worst scenario sensitivity analysis was used in only two occasions.[113, 116]

Six studies[12, 87, 108-110, 113] performed a univariate sensitivity analysis to test how crucial certain study parameters were and how the overall results could vary if those parameters changed. The effectiveness and cost of SCS, the IPG battery life, SCS complication rates, the overall cost of "conventional care" or the location in which implantation took place (i.e. catheter lab versus operating theatre) were some of the parameters tested.

The variables that appeared to have more of an impact on the overall study results included, the cost of the device and its effectiveness, but also SCS complication rates, IPG battery life and adjuvant drug therapy for SCS treatment.

As many as five studies did not perform any kind of sensitivity tests.[40, 92, 112, 114, 115]

4.3.10.2. *Intrathecal analgesic delivery pumps*

None of the two studies[117, 118] on IADP performed probabilistic sensitivity analysis but both used one-way sensitivity testing instead. Kumar et al assessed the impact of changes in the overall cost of the pump, its battery life and complications associated with surgery and reported that the first variable appeared to have the biggest impact on the overall cost recovery period. De Lissovoy et al varied each model input within their respective high and low ranges and concluded that their overall results remained robust despite the changes, concluding that IADP is a cost-effective alternative to usual care" in FBSS patients.

4.3.11. Battery life

4.3.11.1. *Spinal cord stimulation*

All of the six studies that presented a time horizon of five years or above did cover IPG battery depletion, most of which used four years as the average life for the device[12, 108, 109, 113, 116] for their base case scenario, while Kemler et al used 5.8 years.[87] These assumptions were either derived from the literature[116, 121] or taken from manufacturer's data. Five out of these studies performed a sensitivity test varying the length of the IPG unit but in most cases, the results did not change dramatically their overall conclusions, supporting the cost-effectiveness of SCS versus alternative medical treatment in FBBS.[12, 109, 113] For CRPS we find contradicting results and while two studies by the same author reported that their results did not change dramatically when varying the lifespan of the IPG unit,[87, 108] Simpson et al did find that their results were very sensitive to such changes in this specific indication (ICER of GBP 40 017 per QALY gained for a battery life of 3 years).[12] The authors highlight this finding in their evaluation and mention the scarcity of evidence as an important source of uncertainty in this indication.

Two recent studies covering this topic made an additional direct comparison between rechargeable and non-rechargeable IPG units,[108 109] varying only the potential battery life of the non-rechargeable IPG unit (from 1 to 16 years), while fixing the battery life of the rechargeable at nine years. Both studies concluded that the rechargeable IPG system becomes cost-effective at a threshold of GBP 20 000 only when the longevity of the non-rechargeable is below four years. These results are in line with a study published by Hornberger et al in 2008[122] in which they performed a state-transition probability model to compare the overall costs over a patient's lifetime of a rechargeable versus a non-rechargeable SCS system. The study was undertaken in the US from a payer perspective and was built from published literature, assuming an average battery life for the non-rechargeable IPG of 4.1 years and of 17.7 years for the rechargeable one (based on tests from manufacturer). Although the assumptions around the lifespan of the rechargeable device appear to be optimistic, in view of the fixed life span of 9 years set for some rechargeable devices currently in the market, all inputs were tested in a one-way sensitivity analysis which varied the battery life for the non-rechargeable from 3-6 years and that of the rechargeable from 10-25 years. Results appeared to be robust and showed a potential lifetime saving by using the rechargeable IPG device of between US$ 104 000 to US$ 168 833.

4.3.11.2. Intrathecal analgesic delivery pumps

In IADP, De Lissovoy et al[118] used a battery life of four years, while Kumar et al[117] used five years for their base case scenario. Although both studies included the battery life in their sensitivity tests, the latter only tested what would happen if the lifetime of the pump was extended, while the former looked at a worse case scenario in which the battery life was reduced to 3.7 years (44 months). Length of battery life seems to be less of a problem in IADP since they appear to last longer than SCS batteries and thus the potential impact on costs of this factor is smaller.

4.4. Discussion

4.4.1. Spinal cord stimulation

Although in FBSS, most of the evidence published at the time of this review appears to support the cost-effectiveness of SCS versus alternative medical approaches only two trial-based economic evaluations were included in this review for that specific indication.[40, 111] One of them,[111] a US study comparing SCS to re-operation over 3.1 years, reported positive results towards SCS with a 72% probability of being cost-effective at a threshold of US$ 40 000, but its small sample size (n=42) and the allowance for crossing over do represent limitations which should be borne in mind.

The remaining trial-based study in FBSS[40] presented inconclusive results with SCS in combination to "usual" care being more costly but also offering important improvements in patients' EQ-5D scores over time when compared to "usual" care alone. Its most important limitation was the short time horizon of the analysis (i.e. six months), which may be partly responsible for the high costs of SCS. This limitation was recognised by the authors who justified the choice of time frame on ethical grounds: crossing over from one treatment arm to the other needed to be allowed after 6-months.

Three decision analytic models,[12, 109, 113] supported the cost-effectiveness of SCS in this specific indication and while two of them,[12, 109] reported robust results at a threshold of GBP 20 000 (probability of SCS being cost-effective of ≥89% and ≥82% versus CMM and re-operation respectively at this threshold) the remaining[113] showed that SCS was dominant over a patient's lifetime (both cheaper and more effective). A potential limitation of the latter is that the resource and costs used were taken directly from a Canadian study, although they were validated by a panel of European experts.

One observational study that also showed positive results for SCS versus alternative treatment followed, over a 5-year period, patients that were referred for SCS but who finally did not undergo electrode implantation.[116] A further pre and post observational study supported these findings but did not include hospitalisation or implantation costs in their analysis, biasing the results by favouring SCS.[114]

Only one recent observational study[107] showed negative results towards SCS when compared to 'usual' care over a 2-year period both in terms of costs and outcomes. Although the reasons behind the differences in the overall results of this study, when compared to all other published evidence, remain unclear, the fact that it was performed on a very specific population makes the generalisation of its findings to other populations difficult.

In CRPS the three studies identified,[12, 87, 108] displayed positive results for SCS but one of them[12] found that their results remained highly sensitive to changes in both the cost of the device and the battery life of the IPG unit. Only one of these studies[87] consisted of a RCT-based trial over one year (extrapolated to a patient's life time) which compared SCS in combination to physical therapy against physical therapy alone from a societal perspective and concluded that SCS was both cheaper and more effective than PT alone. The remaining two[12, 108] were decision analytic models over a 15-year life span comparing SCS to CMM, which reported ICERs of GBP 3562 per QALY and GBP 25 095 per QALY respectively, for their base-case scenarios.

The evidence found in AP was unclear, with only one pre and post study,[115] showing significantly better outcomes for SCS versus cardiac care followed prior to SCS implantation in terms of lower monthly angina frequency rates (from 14 pre to two post implantation) and reductions in Canadian Cardiovascular Society angina class (from three to two). Costs in this study were higher for SCS. It presented a very low sample size (n=24) and no sensitivity test was performed. A further RCT by Andrell et al[92] in 104 patients comparing SCS to CABG showed significantly lower costs for SCS when compared to CABG, with similar outcomes, showing an advantage for SCS. No sensitivity test was performed in this study. The remaining trial[110] in the same population showed higher costs for SCS and non-significant outcomes and concluded that there was a probability for SCS to be cost-effective at a threshold of GBP 30 000 of just 30%.

The only study found in CLI[112] consisted of a trial based RCT in 120 patients which compared SCS to best medical treatment for a 2-year period. This study showed no differences in outcomes and higher costs for SCS, indicating that the latter is not a cost-effective alternative to best medical practice in patients suffering from CLI. Costs were not discounted and no sensitivity test was performed. High mortality rates made it impossible for all patients to contribute towards the costs over the entire study period and do represent a further limitation of the study.

It is important to note that three of the four models covered in our review[12, 108, 109] consist of 2-stage decision analytic models, carried out from a UK NHS perspective, which follow the same structure over the same time frame (15 years). Furthermore, the main clinical inputs and assumptions for the two models studying FBSS come from the same two trials. That is to say the PROCESS trial for the comparison between SCS and CMM[84] and the North trial for the comparison between SCS and re-operation[39]. Similarly, the main source of clinical data for the two CRPS models was the Kemler trial.[86] QoL data used as inputs in these models reflect, in all cases, data captured by means of the EQ-5D instrument, but while the two evaluations done in FBSS adopted the values reported in the PROCESS trial, the two models on CRPS appeared to have used different sources for their QoL data, with Kemler et al using data from a previous trial completed by the same main author in that specific population,[86] and Simpson et al using values reported by McDermott et al in a cross-sectional survey on neuropathic pain undertaken in 2006 in 602 patients from six European countries.[123] Although these models present important similarities and their global results appear to go in the same direction the specific results obtained are slightly different highlighting the importance of the choice of input sources and assumptions in modelling.

Overall, only six out of the 14 studies included in this review for SCS did not report any conflict of interest[12, 87, 92, 107, 112, 116] while the remaining were industry sponsored or received some input from the industry.

Bearing in mind the low sample size displayed in all studies (less than 160 in all cases) and the non-significance of some of the results the lack of sensitivity analyses in as many as 5 of the studies included in this review is striking.[40, 92, 112, 114, 115]

In addition to this, the impossibility of blinding SCS treatment does incorporate a further bias that lowers the value of the evidence here analysed.

4.4.2. *Intrathecal analgesic delivery pumps*

The two studies included in this review for IADP did show positive results compared to 'usual" care'. One of them,[117] consisted of a trial-based evaluation done over a 5-year period, which showed significantly lower costs for IADP versus "usual" care and better outcomes. The very low sample size (n=67, with only 23 patients on IADP) represent its main limitation. The remaining study on IADP[118] consisted of a modelling exercise which made strong assumptions, in particular regarding the efficacy of SCS versus that of "usual" treatment, and therefore the generilisability of its results remains a challenge. Both studies performed one-way sensitivity testing.

4.5. Key points

There is only low quality evidence on cost-effectiveveness of neuromodulation. However:

- **In patients with FBSS, and based on low quality evidence SCS could to be cost-effective at generally referred thresholds (see Table 7) when compared to conventional care or re-intervention.**
- **In patients with CRPS, and based on low quality evidence SCS used in combination with conventional care or physical therapy could to be cost-effective at generally referred thresholds, when compared to conventional care or physical therapy alone.**
- **In patients with refractory angina pectoris, evidence on cost-effectiveness of SCS is inconclusive.**
- **In patients suffering from CLI there is no evidence of cost-effectiveness os SCS.**
- **The overall reported results on the cost-effectiveness of SCS were especially sensitive to the assumptions made on the costs and the efficacy of the device, the pulse generator battery life-time, the overall costs of adjuvant drug pain therapy and the drug cost of 'usual care'.**
- **In patients with failed back surgery syndrome the scarce available evidence on the cost-effectiveness of IADP is unsufficient to draw any firm conclusions especially given the lack of evidence on efficacy. In these studies, the cost of the pump had the most important consequence on the overall results.**
- **Studies included in this review presented several limitations:**
  - **Population based studies had low sample sizes**
  - **Short time horizons for a chronic condition**
  - **No blinding inherently possible**
  - **No appropriate sensitivity analyses in some of the studies**
  - **Minority of economic evaluations were trial-based**
  - **Many studies were funded by the industry and an additional one received help from the industry for their data analysis**
  - **Transferability of these results to the Belgian context is unclear since prices and hospitalisation costs for SCS and IADP may differ from those displayed in the studies included in this review**

5. BELGIAN REGULATION FOR REIMBURSEMENT

This chapter gives a brief overview of the Belgian regulations for implantation and reimbursement. More details can be found in the appendix and on the relevant websites. Prices cited are 2011 prices.

5.1. Overall legal framework for reimbursement of medical acts

For all reimbursable medical acts in Belgium a so called 'nomenclature' is used and established by RIZIV–INAMI (NIHDI). These are legally binding published numeric codes intended for invoicing and reimbursing medical and paramedical acts (fee for service), pharmaceuticals, as well as other medical services and goods including implants. Changes occur frequently and those changes are communicated to the national health insurance companies through regular letters or in specific billing instructions manuals for health care providers. For the purpose of this chapter and for the data analysis over the years 2002-2009 presented in chapter 7 we use the version applicable during the second half of 2011.

However, Belgian reimbursement nomenclature changes continuously and an up-to-date, but unofficial consolidated version of the current nomenclature and pseudonomenclature is available from RIZIV–INAMI's website.[124]

5.2. Legal framework for implantable devices

Chapter IX of the nomenclature deals specifically with implantable or invasive devices as opposed to extracorporeal prostheses or devices.

In Belgium, several implant categories are legally defined. For neuromodulation the most relevant category is 1, although some spinal cord stimulators happen to be in category 5. Category 1 covers the active implants that depend on an energy source, while in category 5 implants intended for restricted clinical use are grouped meaning that approval from the college of medical directors is needed for reimbursement.

This Belgian category system should not be confused with the European classification concerning medical devices. The European classification system divides implantable devices into four classes according to the associated risk: low, medium, elevated and high risk. A higher risk classification requires a more elaborate assessment by the notified bodies before CE marking can be obtained.

5.3. Reimbursement modalities for implantable devices

The implant supplier (hospital pharmacy) is allowed to bill the patient a so-called delivery margin (Afleveringsmarge / Marge de deliverance). In general, this delivery margin amounts to 10% of the list price of the device, including VAT, but generally limited at € 148.74 for most devices.

RIZIV–INAMI is responsible for publishing the lists of implants accepted for reimbursement and also the additions and revisions decided by the RIZIV–INAMI Insurance Committee. These lists contain the list price of the device, reimbursement amounts, potential patient supplements and delivery margins and from whom (either advisory physician or college of medical directors) approval is needed for reimbursement.

5.4. Implants concerned by this HTA

The SCS and IADP implants concerned by this HTA are listed by category in Table 55 to Table 57 in the appendix. Obviously, other implants may also be used during a procedure. For example, cement may be used during the implantation of a laminectomy electrode.

5.4.1. Lists of implants accepted for reimbursement ('limitative lists')

Nine limitative lists relevant to this HTA were identified. Those limitative lists dealing with spinal cord stimulators show important differences in prices, even within the same category. In the first limitative list for example the prices for a fully implantable (non-rechargeable) device, without the electrodes, range from around € 4000 to around € 10 000. The price of rechargeable devices without the electrodes (third list) is around € 17 000 but for those devices the external charger is billed separately at around € 1500.

These limitative lists contain some apparent inconsistencies, mainly concerning the price of the patient programmers. These inconsistencies have occurred gradually over time due to negotiation processes. Non-rechargeable category 1 spinal cord stimulators, for example, are dispensed with the patient programmer included. This is not the case for category 5 SCS, nor for rechargeable SCS.

In the limitative lists, IADP price is currently almost € 5200 for a constant one and ranges from € 6300 to € 9900 for a programmable variable rate model.

5.4.2. *Warranty periods*

Warranty periods, beyond the legal warranty, differ depending on the type of device. There are currently no additional warranty provisions for non-rechargeable, category 1 & category 5 spinal cord stimulators and their electrodes, for intrathecal analgesic delivery pumps and the associated catheters, nor for other accessories like patient programmers.

For rechargeable neurostimulators there is a warranty period of nine years: a full warranty of five years followed by a four-year pro rata (of remaining years) warranty. However, a full warranty of nine years applies to the charge unit.

These warranty provisions are currently being debated and are expected to change in the future.

5.5. Approved indications, devices and regulations

For the following indications the advisory physician can approve reimbursement for both non-rechargeable SCS and IADP's:

- Neurogenic pain syndromes
- Thromboangiitis obliterans (Buerger's disease)
- Chronic pancreatitis

The general condition of the patient should be no major counter-indication for the implantation or limit its long-term use. Additionally, there is a SCS - IADP mutual exclusion period between Category 1 SCS and/or IADP devices.

The concept of neurogenic pain syndrome is inherently vague and could include various syndromes with a neuropathic aspect. However, it should be noted that an interpretation rule dated 29/7/2005 formally excludes CRPS (and cluster headache) as an approved indication.[125]

The reimbursement of an implanted rechargeable neurostimulator is currently restricted to long-lasting neurogenic pain syndromes in patients that were already implanted a non-rechargeable category 1 spinal cord stimulator that needed replacement due to *'end of (service) life'* within two years after implantation. These limitations for rechargeable SCS devices for a primo-implantation are currently being debated and might change in the future.

In addition, a temporary agreement from 2007 gives the possibility to reimburse SCS in the case of critical lower limb ischemia but under very strict conditions and for a maximum of 50 new patients each year. This reimbursement requires a formal approval by the college of medical directors. According to RIZIV–INAMI sources, this mode of reimbursement was used for only a few cases each year.

More extensive information on indications, device types and regulations can be found in the appendix.

5.6. Prescribers and implanters

These implants can only be reimbursed when prescribed by a specialist physician (R.D. 24.08.1994, Art.35, §2, a-d) and with specific requirements for case documentation as detailed in the appendix.

Different medical acts for the implantation itself require different specialties. More information on specific specialty requirements can also be found in the appendix.

5.7. Implant suppliers and the delivery margin

The Agreements Commission negotiated a national agreement between the implant suppliers and the insurance organisations.

The delivery margin of the hospital pharmacist for implants of categories 1 to 5 amounts to 10% of the sales price (to the hospital), including VAT, in accordance with the implant price specified on the limitative list, and with a ceiling of € 148.74. This ceiling of € 148.74 is calculated for the set of electrodes, accessories (including patient programmer) and stimulator or pump as a whole.

5.8. Approved implanting centres

All surgical procedures described in the previous section, except for thromboangiitis obliterans, need to be performed in a hospital that has a neurosurgical service that effectively operates under the direction of a specialist physician in neurosurgery, and that ensures a permanent emergency service where the patient can present himself at any moment when experiencing problems with the SCS or IADP.

The surgical procedure for thromboangiitis obliterans (also known as Buerger's disease), needs to be performed in a hospital that has a surgical service specialised in vascular surgery that effectively operates under the direction of a specialist physician in vascular surgery, and that ensures a permanent emergency service where the patient can present himself at any moment when experiencing problems with the neurostimulator or pump.

5.9. Trial period

The trial consists in the spinal stimulation or the intrathecal administration of analgesics during at least four weeks, including minimum two weeks at the patient's normal residence.

Evaluation is performed twice; once before the trial period starts and a second time at the end of the fourth week and the trial must be evaluated according to standardised criteria.

The outcome of the trial is considered positive when all of the following criteria are fulfilled:

- A pain reduction ≥50%
- A pronounced reduction of the medication (either by reducing doses, by falling back on lighter analgesics or by stopping medication)
- A significant improvement of the scores on 'daily living activities' and 'quality of life'
- For the indication thromboangiitis obliterans: an increase in walking distance and an improvement or healing of the trophic disturbances

As shown in chapter 6 this trial period of four weeks is much longer than in other countries where it is from 5 days to 2 weeks. In the field fears are expressed those longer trial periods with external devices might increase the inherent risk of electrode or catheter infection. In chapter 7 t is also demonstrated that those longer trial periods do not lead to many so-called *'negative trials'.*

5.10. Drugs approved for intrathecal administration

The specific evaluation of drugs for intrathecal administration was not part of this technology assessment but differences exist between countries about approval and reimbursement of specific drugs approved for IADP.

5.11. Request for reimbursement

The rechargeable and non-rechargeable spinal cord stimulators with their electrodes and accessories as well as the programmable and non-programmable intrathecal analgesic delivery pumps with the exception of their catheter, will only be reimbursed when the advisory physician of the sickness fund has given his approval.

The request for reimbursement of the material needs to be submitted accompanied by a comprehensive medical report drafted and signed by all members of the multidisciplinary team responsible for the implantation and the treatment.

The medical report required to obtain reimbursement needs to contain an anamnesis, a diagnosis, the indication with the multidisciplinary evaluation and the results of the trial as described in the next section. More details about the reimbursement requirements can be found in the appendix.

5.12. Medical acts relevant to this HTA

Several medical acts are relevant to this HTA and are listed in Table 58 to Table 61 in the appendix. This description details the nomenclature applicable during the second half of 2011, the period the data for analysis were retrieved. Important changes were implemented in the medical nomenclature for pain management in January 2012. However, those changes did not affect the indications for neuromodulation that are relevant for this report. For information on the current nomenclature the reader is referred to the relevant RIZIV–INAMI website. [124]

The current list of medical acts related to SCS as shown in the appendix is perceived by many health workers in the field as too limited. This opinion was previously expressed by the Belgian Pain Society as stated in their task force report (see Section 5.15).[126] In analogy with the cardiologic nomenclature available for pacemaker, CRT and ICD implantations, they made several suggestions:

- Differentiation between the percutaneous and surgical implantation act of a trial electrode
- Recognition of the act of replacing an electrode
- Recognition of the act of programming a neurostimulator with measurement and recording of the paraesthesia thresholds and adjustment of the maximum stimulation amplitudes according to a protocol. This is important to delay battery depletion, especially for non-rechargeable neurostimulators
- A specific reimbursement for the multidisciplinary evaluation of the trial period and the drafting of the comprehensive medical report

5.13. Multidisciplinary teams for pain management

The International Association for the Study of Pain (IASP) has issued several recommendations for the management of chronic pain,[8] and in these recommendations the role of a multidisciplinary approach to pain treatment is emphasised. The implant of an SCS or IADP device is normally only considered when more conventional pain therapy fails to provide satisfactory pain relief but also for neuromodulation, this multidisciplinary approach is recommended.

The importance of adequate revalidation after implantation is also stressed., both in literature as during our contacts with the field in Belgium, Indeed, prior to receiving SCS or IADP therapy, almost all patients went through many years of adapting to living with severe chronic pain. However, even when SCS or IADP therapy turns out to be successful to a certain degree at the technical-clinical level, two additional hurdles remain to be taken:

Firstly, patients need to accept and overcome the sensory and psychological discomfort of living with the paraesthesia or numbness induced by the therapy.

Secondly, patients need to fully grasp the opportunity to readjust to a better quality of life and possibly the ability to perform better their daily activities. It should be avoided that they stay with acquired habits and arrangements. Only then, the full benefit of these therapies may be realised.

Therefore a successful implant of a pain management device is considered by experts to be insufficient. To attain the full potential improvements in the patient's physical, psychological, labour and social functioning, the support of a multidisciplinary team is desirable.

As previously mentioned the reimbursement request needs to be accompanied by a comprehensive medical report drafted and signed by all members of the multidisciplinary team responsible for the implantation and the treatment. However, this requirement could become 'pro forma' in practice and does not necessarily require the functioning or the follow-up by a true multidisciplinary team.

5.14. Organisation of pain centres

As mentioned in section 5.8 neuromodulation systems can be implanted in many Belgian hospitals and although there are requirements for the services that need to be available and also for the administrative aspects of the request for reimbursement, there are no formal criteria to recognise such centre as a 'pain centre'. There are also no specific definitions or training criteria for a medical specialism of *'algology'* as there is in some other countries.

However, there are in Belgium a several but temporary initiatives ongoing such as the referral centres for chronic pain, the pilot projects *'Algological function'* and the multidisciplinary pain teams.

In Belgium, nine so-called 'referral centres for chronic pain' have been officially recognised. Seven of these are located in University hospitals and they are all geographically spread over the country. A list of these centres and a summary of the working principles and agreement with the registered referral centres can be found in the appendix.

A multidisciplinary revalidation program can encompass no more than 20 treatment sessions within a period of maximum 12 months. However, these sessions may occur in a shorter time span; e.g. a number of weeks.

Most of the cost of the specialised multidisciplinary diagnosis and that of the multidisciplinary revalidation program are reimbursed.

Patients are referred to the referral centre by their general practitioner or treating specialist physician. The referral is done by means of a referral letter focusing on the pain problem. The referral letter and accompanying documents need to clearly state the anamnesis, the performed medical examinations and the treatment attempts including their results.

In order to promote the collaboration between referral centres and referrers, the agreement provides in a one-time honorarium for the general practitioner or treating specialist physician attending the centre's team meeting concerning his patient. The interventions of the referral centre should be as limited as possible. At the end of a treatment at the referral centre, patients need to be referred back to primary or secondary care with recommendations for further treatment.

A more detailed description and evaluation of those different initiatives on quality and organisation of pain centres in Belgium can be found in a 2011 report from the ministry of health (FOD–SPF).[6]

5.15. Scientific Pain Societies

The Belgian Pain Society (BPS)[c] is the Belgian chapter of the International Association for the Study of Pain (IASP)[d]. The Belgian Pain Society is a multidisciplinary scientific association which assembles the medical and paramedical professionals involved in the management of chronic and acute pain.

The main goals of this association are to support the education about pain treatment and to stimulate pain research and implementation.

In March 2009, the Belgian Pain Society published a task force report entitled 'Spinal Cord Stimulation for Chronic Pain'.[126] That report makes a number of recommendations about the nomenclature, indications, inclusion and exclusion criteria, trial protocols and revalidation. Some of those suggestions were mentioned in this chapter and a few of those suggestions have already been addressed formally through recent nomenclature changes.

Other international societies also have their Belgian or Benelux chapters, such as the previously mentioned International Neuromodulation Society (INS)[e] and the World Institute of Pain[f], that also organises international workshops and accreditations.

Locally the Dutch and Flemish sections on pain management of the societies of anaesthesiology (NVAsP–VAVP) have been instrumental in developing evidence based guidelines on pain management.[99, 127]

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c http://www.belgianpainsociety.org

d http://www.iasp-pain.org

e http://www.neuromodulation.com

f http://www.worldinstituteofpain.org

5.16. Key points

- **The regulation for the reimbursement of neuromodulation devices (SCS and IADP) is at the same time detailed and complex, but also vague since the concept of neurogenic pain can be interpreted differently.**
- **For IADP the accepted indications in Belgium are almost the same as for SCS.**
- **There is a remarkable discrepancy between accepted indications for reimbursement in Belgium and the available evidence for effectiveness. Examples include:**
  - **SCS: CRPS is excluded but there is some evidence for efficacy**
  - **SCS: angina pectoris is excluded but there is some evidence for efficacy**
  - **IADP: neurogenic pain is included but there is very little evidence for efficacy and there is evidence for potentially serious complications**
  - **IADP: cancer pain is not formally included but there is some evidence for efficacy**
- **The multidisciplinary approach is formally regulated but is not always implemented in practice.**
- **Device prices for implantable spinal cord stimulators show important variation even within the same categories. Charge units for rechargeable spinal cord stimulators are billed separately and are quite expensive.**

6. REGULATIONS FOR REIMBURSEMENT IN NEIGHBOURING COUNTRIES

6.1. Introduction

Evidence for effectiveness and cost-effectiveness of neuromodulation is not compelling. Therefore, it could be suspected that different countries handle those uncertainties differently. Therefore, the aim of this chapter is to compare reimbursement regulations for SCS and IADP and the use of this technology in neighbouring countries (France, the Netherlands, Germany, and the United Kingdom) in order to document possible variation of practice and regulation between countries and to identify potential areas for improvement in our country.

Reimbursement information was obtained from official national websites related to health care, contacts with national official organisations and specialised literature. The reimbursement of these devices by private insurers was not analysed in this report.

6.2. France

6.2.1. Overall legal framework for reimbursement

Three main regimes make up the French statutory health insurance (SHI): the general regime, the agricultural regime, and social regime for the self-employed. Apart from these, there also exist very specific regimes.

In 2004, the Union of the national sickness funds (*"l'Union nationale des caisses d'assurance maladie, UNCAM"*) was created, grouping the three main health insurance regimes. UNCAM fulfils several roles:

- It oversees the policy
- It defines the field of reimbursable services
- It fixes the reimbursement amounts

SHI covers, under the various schemes, almost 100% of the resident population and fund three quarters of total health spending. The coverage for outpatient and inpatient care differs.

Covered outpatient care is detailed in three official lists:

- Procedures for health care professionals

- List of reimbursable drugs ("liste des specialites pharmaceutiques remboursables; LSPR")
- List of reimbursable medical devices and health materials (*"liste de produits et prestations remboursables; LPP"*)

For acute hospital care, a Diagnosis Related Group (DRG)-system of payment is applied (*"tarification à l'activité; T2A"*). All hospitals are funded on the basis of "rates per activity", or homogeneous hospital stay groups (*"groupes homogènes de séjour; GHS"*). All patient stays are classified in one of the approximately 2200 homogeneous patient groups (*"groupes homogènes de malades; GHM"*) and an associated GHS.

Positive lists are applied for procedures paid outside the DRG system. There is a specific list for drugs (*"liste des spécialités agréées aux collectivités; LSAC"*) and special lists for expensive and innovative drugs and devices that can be paid in addition to the DRG tariffs (*"liste des produits et prestations pris en charge en sus des prestations d'hospitalisation"*). Medical devices in this list are also included in the LPP.[128]

6.2.2. Legal framework and reimbursement modalities for implantable devices

Introduction of implantable medical devices to the market is subject to obtaining CE marking delivered by a notified body, and to a communication of the introduction to the National Security Agency for Medicines and Health Products (L'Agence nationale de sécurité du médicament et des produits de santé[g]; ANSM; previously called *"Agence Française de Sécurité Sanitaire des Produits de Santé"; AFSSAPS*). The ANSM will then be in charge of the monitoring of the market.

To be reimbursed, implantable medical devices must be included in the LPP. Inclusion in the LPP is decided by the Ministry of Health under the guidance of the National Commission for the Evaluation of Medical Devices (*"Commission nationale d'évaluation des dispositifs médicaux et des technologies de santé; CNEDIMTS"*), that assesses the clinical benefit of the device. The registration on the list depends upon the service rendered by the product ('service rendu'), assessed essentially by the therapeutic and technical effect of the product, the safety, the comparison with other available alternatives, the severity of the disease or handicap addressed by the product, and other public health considerations such as the impact on the quality of life. Since 2008, the use of economic evaluation has also been introduced but it remains unclear what will be its exact role and future implementation.

Then, if listed, the Economic Committee for Health Products of the Ministry of Health (*"Comité économique des produits de sante; CEPS"*) finalises the conditions for reimbursement and determines the reimbursement tariffs according to the guidance of the CNEDIMTS. The public price of devices included in the LPP is limited to the LPP reimbursement tariffs.

For hospitalised patients, medical devices cannot be charged to the patient. They are covered by the GHS system of payment. However, as specified above, implants can be reimbursed to the hospital in addition to the GHS reimbursement if they are included in the special list.[128]

6.2.3. SCS reimbursement criteria

6.2.3.1. Implants accepted for reimbursement and coverage

Implantable SCS neurostimulators and electrodes included in the LPP (and in the special list) are described in the appendix in Table 62 (non-rechargeable SCS), Table 63 (rechargeable SCS) and Table 64 (electrodes).[129] As stated above, prices in this table only cover the implant. Procedures as well as other hospital costs are covered by the DRG system of payment. For implants not included in the LPP, they will only partially be covered by the DRG system of payment.

6.2.3.2. Approved indications

Reimbursement of SCS on top of the DRG system is assured for patients suffering from:

- Intractable chronic pain of neuropathic origin, upon failure of other therapeutic measures and secondary to:
  - Chronic radicular pain (sciatalgia, cruralgia, cervical brachialgia)
  - Peripheral nerve injury, of post-traumatic or postsurgical origin
  - Amputation (algo-hallucinosis)

[g] Since May 1, 2012

- Complex regional pain syndrome (CRPS) (reflex sympathetic dystrophy, causalgia with peripheral nerve injury)

- Ischaemic pain due to peripheral artery disease (PAD) like arteritis of stage III or IV

After failure of SCS, the following alternatives can be considered:

- Deep brain stimulation
- Implantable pumps for the intrathecal injection of analgesics (IADP)
- Surgery of afferent sections

Refractory angina and diabetic neuropathy are not reimbursed indications.[129]

6.2.3.3. Prescription and use modalities

Reimbursement is subject to several conditions:

- Indications must be properly validated. Such validation implies:
  - An assessment of psychosomatic factors that may affect the status of the patient and justify his exclusion
  - Assure patients compliance
  - Sufficient management of physical patient conditions for the implementation of the device, including a satisfactory integrity of the sensory pathways in the dorsal columns (satisfactory somatosensory evoked potentials)
  - A stimulation trial period prior to the implantation, with a minimum duration of 10 days that demonstrates a pain reduction ≥50%. This test is preferably performed in an ambulatory care corresponding to the patients' residence
- Care must be managed by a multidisciplinary intractable chronic pain team within the context of 'pain consultations' *('consultation douleur')*.[h]

[h] The team must respect the modalities on the management of chronic pain described in the information circular DGS / DH No. 94 / 3 from 07-01-1994 and the structure must appear on the list maintained by the regional hospitalization agencies in accordance with information circular DGS / DH No. 98/47 of 04-02-1998.

  This team is in charge of the validation of the indication, the assessment of results of the stimulation-test and the post-implementation monitoring
- The implant must be placed by a team that is trained to perform this procedure
- A long-term follow-up must be performed in the context of "pain consultations" to adapt stimulation parameters, to adapt pharmaceutical treatments and to reach the objectives of pain reduction

Moreover, for the reimbursement of rechargeable spinal cord stimulators, patients must require high stimulation level, meaning:

- An expected device service life of less than 30 months after a primo implantation, or
- A stimulation threshold higher than 3.5V at the end of a stimulation trial for new patients

All primo-implant rechargeable SCS devices have the status of exceptional product (Article R. 165-1 of the Code of Social Security, last paragraph). The reimbursement modalities of these products are fixed by an order of the Minister of Social Security and include a sheet containing therapeutic information established by the CNEDIMTS (such as indications, prescription and use modalities, treatment duration, etc.). These devices must be prescribed with a specific prescription format, by which the prescriber certifies the adequacy to the requirements contained in the information sheet.[129]

6.2.4. IADP reimbursement criteria

6.2.4.1. Implants accepted for reimbursement and coverage

IADP included in the LPP (and also in the special list) is described in Table 62. It should be noted that non programmable implantable pump (3461026) and programmable implantable pump (3446771) for perfusion with continuous flow were removed from the list in 2009. Only the programmable implantable pump for perfusion with variable flow stays in the list.[129] Therefore, if a non programmable implantable pump is implanted, its cost will only partially be covered by the DRG system of payment.

6.2.4.2. *Approved indications*

Intrathecal analgesic delivery pump are approved for:

- The treatment of severe chronic pain refractory to opioids or non opioids administered systemically.[129]

6.2.4.3. *Prescription and use modalities*

- Analgesics must have received a market authorization for this route of administration and be included in the list of reimbursable drugs (LSPR). Drug use modalities defined in the LSPR must be followed
- Patient follow-up for the management of pain should be performed by a multidisciplinary team including a surgeon and an expert physician recognised by a pain clinic
- The pump is implanted after completion of tests to demonstrate the clinical efficacy of intrathecal analgesics[129]

6.2.5. *Number of procedures performed*

The number of procedures in France was estimated by the number of reimbursements for the implants (LPP codes), making it impossible to differentiate between IADP (analgesic) and Baclofen pumps.

Table 8 – Evolution of the number of SCS-related procedures in France

	2006	2007	2008	2009	2010
Non-rechargeable SCS	401	371	364	302	396
Rechargeable SCS	0	0	49	110	127
Total	401	371	413	412	523
Per capita (/ 1 000 000)	9.30	8.30	9.19	8.87	11.35

Source: Ameli 2012[130]

Table 9 – Evolution of the number of IADP-related procedures in France

	2006	2007	2008	2009	2010
Non programmable IADP and Baclofen pumps	13	15	13	2	0
Programmable Baclofen pumps (continuous debit)	55	60	40	30	1
Programmable IADP and Baclofen pumps (variable debit)	0	0	0	34	78
Total	68	75	53	66	79
Per capita (/ 1 000 000)	1.58	1.68	1.18	1.42	1.72

Source: Ameli 2012[130]

6.3. The Netherlands

6.3.1. *Overall legal framework for reimbursement*

In the Netherlands, a new private health insurance system with social conditions was established in 2006. Under the new Health Insurance Act ("Zorgverzekeringswet"), each resident is obliged to take out health insurance, insurers are obliged to accept each resident in their area of activity and a system of risk equalization has been set up to prevent risk selection. Even while basic health insurance is compulsory, about 1% of the population is uninsured.

A standard package of essential healthcare must be provided by all insurers. This basic package is determined by criteria such as proven efficacy, cost-effectiveness, and the need for collective financing. In 2008, this package included:

- Medical care provided by GPs, hospitals, specialists and midwives
- Hospital stays

- Dental care for individuals aged under 22 (for older people only specialist dental care and a set of false teeth are covered)
- Medical aids and devices
- Pharmaceutical care
- Maternity care (midwife care and maternity care assistance)
- Transport of sick people by ambulance or taxi
- Paramedical care (physiotherapy, exercise therapy, dietary advice, speech therapy)
- Mental care

For some treatments, exclusions have been defined (e.g. there is a maximum number of sessions for allied care and some elective interventions such as aesthetic plastic surgery are not reimbursed). Moreover, a yearly deductible of € 155 (in 2009) is imposed (i.e. an amount of expenses that must be paid out of pocket before the insurer will pay any expenses) for all care of individuals aged 18 years or more except for GP care, obstetric care, maternity care and dental care under the age of 22.

For hospitals care, an elaborate DRG system called Diagnosis and Treatment Combinations (Diagnose Behandel Combinaties, DBCs) has been in place since 2005. Compared to the traditional DRG system in other countries, this DBC system allows for more than one DBC per patient and therefore provides more flexibility in the case of multiple morbidity. However, in practice the results of this system were disappointing and this lead to a new reform of the system in 2011 changing DBC into DOT (DBC Op weg naar Transparantie).[131]

6.3.2. Legal framework and reimbursement modalities for implantable devices

The introduction of medical devices to the market is subject to CE marking delivered by a notified body. Concerning the reimbursement of medical devices, there are several arrangements. Non-implantable medical devices for outpatient use are in general included in a limitative list to which new categories can be added to the list each year on the advice of the College of Care Insurances ("College Voor Zorgverzekeringen" (CVZ)).

Implantable medical devices and non-implantable medical devices that need supervision by a medical specialist fall under the open system for medical specialist care. To be included in the basic healthcare package, medical specialists care have to follow evidence-based medicine (EBM) standards ('stand van de wetenschap en praktijk') or, in the absence of such standards, must be considered as reasonable and adequate care ('verantwoorde en adequate zorg en diensten') within the profession. In order to evaluate this, CVZ has developed an evaluation framework available on their site (http://www.cvz.nl/resources/rpt0711_stand-wetenschap-en-praktijk_tcm28-25006.pdf). The difference between an open system and a closed system is that they do not have to evaluate everything before it can enter the system. Currently, they only assess interventions for which there are doubts whether the intervention meets the EBM standards.[132]

6.3.3. SCS reimbursement criteria

Since 1998, the Netherlands has a national quality system for neuromodulation techniques (SCS and perispinal administration of drugs using IADP). The management of the quality system was previously done by the National Foundation on Quality in Neuromodulation (*"Stichting Landelijk Kwaliteitssysteem Neuromodulatie"*; SLKN).[133] In 2007 the Netherlands Society for Neuromodulation ("*Vereniging voor Neuromodulatie Nederland"*; VvNN) was founded, grouping the Dutch healthcare providers involved with neuromodulation. Apart from its regular scientific agenda, this organisation is also involved in frequent consultation with all stakeholders, including other healthcare providers in the Netherlands, health care payers, scientific societies and other (www.neuromodulatie.com).

6.3.3.1. Implants accepted for reimbursement and coverage

The choice of the implant for eligible patients will be determined by the neuromodulation centre, in consultation with the patient. DBC codes and related amounts in 2011 can be found in Table 66 in the appendix.

6.3.3.2. Approved indications

CVZ only gives an advice on SCS for patients with refractory angina pectoris and failed back surgery syndrome (FBSS). They concluded that SCS must be included in the basic package for refractory angina pectoris and for FBSS if the requirements defined by the VvNN are followed (see 6.3.3). Official indications recognised by the VvNN for SCS after failure of conventional treatment or important side effects are:

- FBSS;
- Complex regional pain syndrome I (CRPS)
- Phantom pain
- Peripheral nerve injury
- Spinal lesion
- Traumatic brachial plexus injury
- Refractory angina pectoris
- VvNN also specified that patients must experience chronic pain ≥ 50 mm on a 0–100 mm visual analogue scale

6.3.3.3. Prescription and use modalities

SCS and IADP are only reimbursed in a limited number of centres (around 30 in 2012) and indications (see 6.3.3.2 recognised by the VvNN. Centres who want to perform SCS and IADP must notify the VvNN. A minimum number of interventions per centre are required: 20 surgical interventions (including revision and battery changes) per year for SCS and 8 pumps every 2 years for IADP. After approval by the VvNN, they can start negotiations with the insurers.

Treatment phases determined by the VvNN include:

1. Determination of treatment eligibility (including a psychological assessment)
2. The pilot phase, e.g. for SCS, a stimulation test with an external battery to determine whether the patient experiences sufficient pain relief (minimum 1 week)
3. A registration (not mandatory) for quality assessment

Treatment must be given by a multidisciplinary team.

6.3.4. IADP reimbursement criteria

IADP is indicated for chronic pain. Approved indications (in case of chronic pain) and use modalities are the same than for SCS.

6.3.5. Number of procedures performed

It is estimated that around 900 SCS and 20 IADP are implanted annually for the management of chronic refractory pain, corresponding to a per capita of 54.3 and 1.4 per million respectively. According to the register of the VvNN (ProMISe), around 75 pumps are implanted annually for spasticity and chronic pain together or a per capita of 4.5 per million (source: Robert van Dongen, president of VvNN, personal communication, 2012).

6.4. Germany

6.4.1. Overall legal framework for reimbursement

Germany is a federal republic composed of 16 states (=Länder). With the exception of permanent civil servants and the self-employed, Germans who earn less than a certain yearly gross salary (€ 50 850 in 2012) must join one of the statutory sickness funds. Those earning more than this mandatory insurance threshold may opt out of the state system and buy private insurance, even if many of them decide to remain in the state system.[134, 135]

German sickness funds are mainly financed by contributions set as a uniform percentage of income. Premiums are deducted from pay packages with employers and employees sharing equally the costs.[134]

Germans are free to choose their insurer, and 'open' sickness funds must accept any applicant. Sickness funds fall into six groups:

- General regional funds, the largest health insurance organization in Germany ("Allgemeine Ortskrankenkassen"; AOK)
- Substitute funds ("Ersatzkassen")
- Company-based funds ("Betriebskrankenkassen"; BKK)
- Guild funds ("Innungskrankenkassen"; IKK)
- Farmers funds ("Landwirtschaftliche Krankenkassen"; LKK)
- Miners' fund ("Knappschaft")

The statutory health insurance framework and co-payment levels are set by federal law but most decisions on the contents of the uniform benefits package and the delivery of curative health services are made through joint negotiations between the providers (associations of physicians and/or dentists and/or the Hospital Federation) and the payers (associations of sickness funds) at both regional and national levels.[134, 135]

Hospital Funding in Germany is regulated by the "Hospital Financing Act". Investments for hospitals are financed by the states (*"Länder"*) and operating costs of hospitals (medical goods, personnel costs, etc.) are financed by the sickness funds (plus private insurers). Operating costs are covered by a prospective budget negotiated in advance for one year with the Länder associations or representatives of the sickness funds. Optional before 2004 but compulsory since then, the inpatient payment system is based on Diagnosis-Related Groups (DRG). The German DRG (G-DRG) system is applicable to all patients (members of the statutory health insurance (SHI), private insurance or self-paying patients) and to all hospital services, with the major exception of psychiatry, psychosomatic medicine, or psychotherapy services. For those services, the G-DRG system will be set up in 2013. Compared with other countries, this system gives a great importance to the indication and procedure performed. The DRG is determined by the diagnosis, procedures, co-morbidity, clinical severity, patient age, etc.[134, 135]

The G-DRG system is maintained and annually updated[i] by the Institute for the Hospital Remuneration System ("Institut für das Entgeltsystem im Krankenhaus"; InEK). The diagnostic (ICD-10-GM) and procedural codes ("Operationen- und ProzedurenSchlüssel"; OPS) employed by G-DRG are maintained and annually updated by the German Institute of Medical Documentation and Information ("Deutsche Institut für Medizinische Dokumentation und Information"; DIMDI).[136]

Relative cost weights for each DRG as well as fixed price supplemental fees are determined at the national level. The hospital reimbursement is then established (i) by multiplying its case-mix by the state-wide base rate ("Landesbasisfallwerte") and (ii) adding the negotiation of other budget components such as new innovation supplemental fees (NUB for new examination and treatment methods), individual (temporary) supplemental fees, etc. The state-wide base rate is negotiated in every state. In 2012, the negotiated state-wide base ranged from € 2910 to € 3175.75, with an average of € 2990. The 2009 Hospital Financing Reform Act further modifies hospital financing in Germany and state-wide base rates are programmed to converge to a nation-wide base rate by the year 2015.[134, 136, 137]

6.4.2. Legal framework and reimbursement modalities for implantable devices

The licensing of medical devices (CE label) is the responsibility of notified bodies. The Hospital Care Committee of the Federal Joint Committee ("*Gemeinsamer Bundesausschuss"; G-BA*, i.e. the supreme decision-making body of the so-called self-governing system in Germany) is in charge of decisions about hospital coverage based on health technology assessment but only decides on benefit exclusion (not on benefit inclusion). They can be helped by the Institute for Quality and Efficiency (*"Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesenis"; IQWiG*) which provides evidence at the request of the Federal Joint Committee or the Federal Ministry of Health.[135]

Financing of medical devices is usually part of the DRG (flat rate per case) or supplemental fee (see below, ZE). The InEK has also created an "on-top" funding process for innovative diagnostic and treatment procedures for a duration of maximum one year, i.e. the process for new diagnostic and treatment method ("Neue Untersuchungs- und Behandlungsmethoden"; NUB). Every hospital can apply to the InEK separately for this *'on-top'* payment for technologies that have just been introduced in Germany. If NUB submission gets InEK approval, the amount of the "on-top" payment can be negotiated between the successful hospital applicants and the SHIs. The amount differs between hospitals.[136]

For expensive drugs, medical devices and procedures, supplemental fees (Zusatzentgelte, ZE) on top of the G-DRG flat rate are also provided. The supplemental reimbursements are generally listed in the case fees catalogue ("Fallpauschalen-Katalog") of the running year but are generally not available to every hospital. Hospitals have to negotiate the type and number of ZEs with the SHIs.[136]

[i] using data from the previous two years

6.4.3. SCS reimbursement criteria

6.4.3.1. Implants accepted for reimbursement and coverage

SCS are considered as complex/expensive procedures/devices and specific OPS codes have been created. Supplemental reimbursements listed in the case fees catalogue of 2012 specific for SCS are listed in Table 67.[138] As specified in this table, rechargeable neurostimulators have to be negotiated on a hospital-by-hospital basis in contracts between hospitals and sickness funds until InEK is able to calculate fixed price supplemental fees.

6.4.3.2. Approved indications

No exclusion of indications has been defined. SCS are covered for all kind of indications. According to the Institute for Medical Knowledge Management (Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften; AWMF) the following indications should be considered (considered as good clinical practice, German S3 guidelines) following unsuccessful conservative therapy:[139]

- Neuropathic pain:
  - Chronic radiculopathy in connection with FBSS
  - CRPS
  - Other neuropathic pain (such as phantom pain, stump pain, diabetic polyneuropathy, post-herpetic neuralgia, brachial plexus injury)
- Ischemic pain:
  - PAD
  - Angina pectoris

They also added which clinical symptoms cannot be successfully treated by SCS, i.e. pain in complete paraplegia syndrome, atrophy/injury of the sensory pathways of the spinal cord or cancer pain.

6.4.3.3. Prescription and use modalities

According to the AWMF, the following stages should be completed:[139]

- Determination of treatment eligibility: review of the previous conservative treatments and neurological, psychological, psychosomatic or psychiatric evaluation of the patient by a multidisciplinary team (a neurosurgeon, a pain therapist, a psychiatrist/clinical psychologist and, depending on the pain syndrome, a neurologist, a cardiologist, or an angiology/interventional radiologist/vascular surgeon)
- The pilot phase, i.e. a stimulation test with one or two electrodes and an external battery to determine whether the patient experiences a sufficient pain relief. They considered that a test duration of 6 - 12 days seemed appropriate. They defined the following conditions for a permanent implant:
  - ≥50% pain reduction (conditio sine qua non)
  - Improvement of patient's mood or quality of life
  - A desire expressed by the patient to reduce medication
  - A desire of the patient to be implanted
- The permanent implantation phase. Implentation should only be carried out by a multidisciplinary team in experienced therapy centers which are in a position to deal with potential complications. A mandatory certification as pain center to manage these patients would be desirable in the future
- The post-implantation phase, including adjustements of the stimulation parameters according to the patient's needs, careful consideration of reduction or even withdrawal of medication, and determination of the follow-up intervals by the treating physician and a referal physician
- The follow-up phase / quality assurrance phase, including an assessment of safety and effectiveness in the long term by a working group on Neuromodulation (NeMoQM)), a continuous adjustment of the stimulation parameters to the patient's needs, the control of electrodes' position and, if needed, a surgical revision. Accompaning measures such as physiotherapy or relaxation exercices could also be advised

6.4.4. IADP reimbursement criteria

6.4.4.1. Implants accepted for reimbursement and coverage

IADP is considered as a complex/expensive procedure/device and specific OPS codes have been created. Supplemental funding listed in the case fees catalogue of 2011 specific for IADP are listed in

Table 68.[138] As specified in this table the reimbursement of some pumps has to be negotiated on a hospital-by-hospital basis in contracts between hospitals and sickness funds

6.4.4.2. Approved indications

No indications are excluded from reimbursement. According to the German Society for Pain Management ("Deutsche Gesellschaft für Schmerztherapie"), this treatment is indicated for patients with chronic pain, where an oral drug therapy as part of a multimodal treatment was unsuccessful for a long time or associated with significant side effects (only for patients with good compliance).[140]

6.4.4.3. Prescription and use modalities

According to the German Society for Pain Management, an individual psychiatric / psychological assessment should be performed, followed by a trial period. A significant pain reduction and improved load capacity should be detected in this test phase. The indication for implantation should be carried out by an interdisciplinary team.[140]

6.4.5. Number of procedures performed

The number of procedures in Germany was estimated using the procedure codes 5-039.e0, 5-039.e1, 5-039.e2, 5-039.f0, 5-039.f1, 5-039.f2 for SCS (i.e. SCS implantation or replacement) and 5-038.40, 5-038.41, 5-038.4X for implantable drug delivery pumps (implantation or replacement) for 2010. This number was 957 for SCS (per capita 11.70 per million) and 1073 for IADP (13.12 per million).[141]

6.5. UK

6.5.1. Overall legal framework for reimbursement

In the UK, every legal resident is covered by the National Health Service (NHS) which is mainly funded by taxes. Except for some pharmaceutical prescriptions, optical and dental services charges, health services are provided freely by local NHS organizations. Primary Care Trusts (PCTs) are responsible for commissioning primary, community and secondary care services for their local population.

Since 2004, a new reimbursement system for hospital care was set up, known as the "Payment by results" system. The volume of activity for the next calendar year is planned by negotiation contracts between primary care trusts and health care providers. Choices are based on guidelines provided by other national organizations such as the National Institute for Clinical Excellence (NICE).

Prices of inpatient and day-care activity are determined according to national tariffs for each Healthcare Resource Group (HRG). No distinction was made in the tariffs between elective inpatient stays and day-care, giving a clear incentive for day-care whenever possible. The HRG process takes into account different factors such as primary and secondary procedures; primary, subsidiary and secondary diagnosis; age; gender; length of stay etc.[142-144]

6.5.2. Legal framework and reimbursement modalities for implantable devices

Introduction of medical devices to the market is subject to the CE marking[j] delivered by a notified body and to a registration of the details concerning the medical device to the Medicines and Healthcare products Regulatory Agency (MHRA). The MHRA also conducts post-marketing surveillance.

NICE only appraises technologies that have been identified through a topic selection process approved by ministers of health (the 'NICE work program') and the NHS is legally obliged to provide funding and resources

[j] Studies involving non-CE marked medical devices carried out in the UK may be regulated as clinical investigations under the Medical Devices Regulations 2002 and require approval from the UK Competent Authority.

for all medicines and treatments that have been recommended by NICE technology appraisals. Technologies considered as standard clinical practice are not included in the NICE program. For new technologies not yet appraised by the NICE, trusts can fund the development and on-going costs of these new technologies either from surplus income received under the Payment by Results system, or from the agreed funding of the costs using a pass-through payment (additional payment for use of a particular device, technology or drug over and above the relevant tariff reimbursement). Funding of medical devices is included in the HRG tariffs but some of them can be excluded for example because the distribution of the device within the relevant HRG is not even across providers and could cause heterogeneity. In case of exclusion, funding is locally negotiated. Moreover, cost and national volume for the excluded item as well as tariffs for the relevant HRG are adjusted to ensure that the effect of the exclusion is cost neutral.[145]

6.5.3. SCS reimbursement criteria

6.5.3.1. Implants accepted for reimbursement and coverage

According to the NICE guidance TA 159 from 2008,[104] the choice of the implant should be based on the complexity of pain pattern and the amount and intensity of stimulation required. It was recognised that for people with complex pain patterns, complex devices may be more appropriate because of a more complete response to the pain and a greater device longevity requiring less frequent re-intervention.

However, if different SCS systems are likely considered to be equally suitable for a person, the least costly should be used. Assessment of cost should take into account acquisition costs, the stimulation requirements, the anticipated longevity of the system, and the support package offered.[104]

The procedure is covered by the DRG system of payment but the spinal cord stimulator is excluded and requires locally negotiated tariff/volume.[146] Procedures for SCS are also indicators of specialised activity (see Table 69).[147]

It should also be noted that a new HRG label more specific to SCS has been created, i.e. AB07Z Insertion of neurostimulator or intrathecal drug delivery device in place of AB01Z Complex Neurosurgical Pain Procedures (tariffs not yet determined).[148]

6.5.3.2. Approved indications

According to the NICE guidance TA 159, SCS is recommended for:

- Adults with chronic pain conditions of neuropathic origin (especially FBSS or CRPS I) and
- Who continue to experience chronic pain (≥ 50 mm on a 0–100 mm visual analogue scale) for at least 6 months despite a standard pain management programs (physiotherapy guided exercise, maximal analgesia and muscle relaxants, psychological treatment)
- They found evidence for FBSS and CRPS but concluded that the use of SCS may be extended for all chronic pain conditions of neuropathic origin if the prescription and use modalities defined in section 1.5.3.3. are followed

SCS is however not recommended as a treatment option for adults with chronic pain of ischaemic origin, except in the context of research as part of a clinical trial designed to generate robust evidence such as on pain relief, functional outcomes and quality of life.[104]

This recommendation was reviewed in January 2012 and it was concluded that there has been no new evidence that would affect the recommendation.[149] A new review will be done at the end of 2013 when more evidence on the use of SCS for the treatment of chronic pain of ischaemic origin becomes available (the RASCAL study).

6.5.3.3. Prescription and use modalities

According to the NICE guidance:[104]

- The person has to be assessed by a multidisciplinary team experienced in chronic pain assessment and management of people with SCS devices
- People must successfully complete a stimulation trial by implanting the electrode(s) and leads with a temporary external device. The duration of this stimulation trial, however, is not defined. This stimulaton trial

will assess several outcomes including the tolerability and the degree of pain relief likely to be achieved with full implantation. This assessment must take into account the person's disabilities (such as physical or sensory disabilities), or linguistic or other communication difficulties. In these cases, the testing procedure may be modified or alternative tests may be used

6.5.4. IADP reimbursement criteria

6.5.4.1. Implants accepted for reimbursement and coverage

No guidance has been given by NICE concerning IADP. They only stated that Intrathecal Baclofen pump implantation is an established procedure that does not fall within the Program's remit because they are considered standard clinical practice with an efficacy and safety profile that is sufficiently well known.

The procedure is covered by the DRG system of payment but the intrathecal drug delivery pump itself is excluded and requires locally negotiated tariff/volume.[146] Procedures for IADP can also be an indicator of specialised activity if combined with pain ICD-10 codes (see Table 70).[147]

It should also be noted that a new HRG label more specific for IADP has been created, i.e. AB07Z Insertion of neurostimulator or intrathecal drug delivery device in place of AB01Z Complex Neurosurgical Pain Procedures (tariffs not yet determined).[148]

6.5.4.2. Approved indications

The British pain society has published recommendations of good clinical practice on intrathecal drug delivery for the management of pain and spasticity in adults. The three major categories of application were considered, i.e. chronic non malignant pain (CNMP), cancer pain, and spasticity. For CNMP, they cited the following: [43]

- Nociceptive pain, particularly mechanical back pain that has not responded to stabilisation procedures
- Mixed cases of nociceptive and neuropathic pain
- And cases of widespread pain (e.g. back and bilateral leg pain)

However, they specified that for CNMP there is currently no randomised controlled trial evidence but only supportive prospective open studies.

6.5.4.3. Prescription and use modalities

The British pain society recommended the following modalities:[43]

- To perform a comprehensive physical and psychological assessment of the patient
- To perform a trial of intrathecal therapy before the permanent implantation. In the Walton Centre for Neurology & Neurosurgery NHS Trust for instance, the trial will last between 5 and 10 days in hospital
- To perform the implantation by a multidisciplinary team, including the implanter, typically a pain specialist or neurosurgeon (or easy access to a neurosurgeon in case of complications), nurse specialists, pharmacists, psychologists and physiotherapists as appropriate
- To provide adequate arrangements for ongoing care such as programme changes and refill attendances by a multidisciplinary team and a relevant infrastructure. Refill intervals should be determined by the stability of the drug
- To consider cognitive behavioural therapy and to educate the primary care team and the patient's family

6.5.5. Number of procedures performed

A study performed from Hospital Episode Statistics (HES) in England suggests that there have been 1050 SCS-related procedures in 2010-2011. Even if the number of procedures has slightly increased after Nice guidelines 2008 (see Table 10), the study has shown that only a quarter of the chronic pain population seems to be currently treated with SCS therapy. Beside this low penetration rate, the study has also shown an unjustified large variation of implant rate among centres (9 per million in one region compared with 32 per million in another, with an average rate at 21.5 procedures per million across NHS England). Moreover, among the approximately 60 centres offering SCS, around only 35 centres are undertaking more than five procedures per year.[150]

According to a personal communication (Dr. Simon Thomson, president of the International Neuromodulation Society), approximately 600 pumps (9.7 per million) are implanted annually in UK, i.e. around 500 for spasticity (8.1 per million) and around 100 for chronic pain (1.6 per million). According to HES statistics in England, 6.4 implantations of intrathecal drug delivery pumps (code A54.3) per million were performed in 2010-2011 in England.[151]

Table 10 – Evolution of the number of SCS and IADP related procedures in England (based on procedure codes A48.3 and A54.3)

	2005-2006	2006-2007	2007-2008	2008-2009	2009-2010	2010-2011
SCS A48.3 Insertion of neurostimulator adjacent to spinal cord	695	645	771	956	971	871
IADP A54.3 Implantation of intrathecal drug delivery device adjacent to spinal cord	-	296	310	369	379	335

Source HES statistics[151]

6.6. Discussion

6.6.1. Overview of the situation in different countries

In the investigated countries, different indications, utilisation rules and reimbursement mechanisms apply. An overview of the situation in different countries is given in Table 11 and compared to the situation in Belgium.

This overview must be used with caution since terms and definitions may differ between countries. Missing information does not always mean that it is not considered in the country but can also mean that no information was found. For all countries the number of implants mentioned is a combination of first implants and replacements since it is difficult to differentiate between both.

Table 11 – Summary of indications, utilisation rules, reimbursement mechanisms and number of procedures

	Belgium	France	The Netherlands	Germany	UK
Implant choice	Included in limitative list For rechargeable SCS: • If service life < 2 year after a primo implantation	Included in the LPP For rechargeable SCS: • Device service life < 30 months after a primo implantation; or • a stimulation threshold > 3.5V at the end of the stimulation trial	Decision made by the centre after negotiation with the insurers	For rechargeable SCS: only accorded on a hospital by hospital basis after negotiations between the hospital and the sickness funds.	Decision is based on the complexity of pain pattern and the stimulation threshold. In case of equally suitable devices, the least costly must be chosen.
Indications: neuropathic pain	Long lasting neurogenic pain syndrome. Specific causes of neurogenic pain are not formally defined, but: • FBSS: in practice • CRPS: excluded • Other (if accepted by advisory physician)	Intractable chronic pain of neuropathic origin secondary to: • Radicular pain • CRPS • Phantom pain • Peripheral nerve injury	Intractable chronic pain of neuropathic origin secondary to: • FBSS • CRPS • Phantom pain • Peripheral nerve injury • Traumatic brachial plexus injury • Spinal lesion	Intractable chronic pain of neuropathic origin secondary to: • FBSS • CRPS • Phantom pain • Brachial plexus injury • Diabetic polyneuropathy • Post-herpetic neuralgia • Other	Intractable chronic pain of neuropathic origin secondary to: • FBSS • CRPS • Other
Indications: ischaemic pain	Ischaemic pain due to: • Thromboangiitis obliterans • PAD (if accepted by college of medical directors, rare)	Ischaemic pain due to: • PAD	Ischaemic pain due to: • AP	Ischaemic pain due to: • PAD • AP	Only in research
Indications: other	Chronic pancreatitis				

	Belgium	France	The Netherlands	Germany	UK
Specific indications for IADP	Same as for SCS (see above)	Severe chronic pain refractory to opioids or non opioids administered systemically	Same as for SCS (see above)	Chronic pain, where an oral drug therapy as part of a multimodal treatment was unsuccessful for a long time or associated with significant side effects (only for patients with good compliance)	Nociceptive pain, particularly mechanical back pain that has not responded to stabilisation procedures Mixed cases of nociceptive and neuropathic pain, Cases of widespread pain (e.g. back and bilateral leg pain).
Utilisation rules	After failure of conventional treatment but with explicit clinical rules. Prescription by a specialist + approval by an advisory physician based on a full medical report containing an anamnesis, diagnosis, indication, a multidisciplinary evaluation and the results of the stimulation test	After failure of conventional treatment but with explicit clinical rules. Validation of the indication (including an assessment of psychosomatic factors and of organic conditions)	After failure of conventional treatment but with explicit clinical rules. Determination of treatment eligibility (including a psychological assessment)	After failure of conventional treatment but with explicit clinical rules. Determination of treatment eligibility (neurological, psychological, psychosomatic or psychiatric evaluation)	After failure of conventional treatment but with explicit clinical rules. Determination of treatment eligibility
Stimulation test	Min 4 weeks with at least 2 weeks extramural (at the patient's home) Pain reduction of ≥50% Pronounced reduction of medication Significant improvement of the daily living activities and quality of life scores	10 days Pain reduction ≥50% Preferably in an ambulatory care setting where the patient returns home	Min 1 week	6 - 12 days seem appropriate ≥50% pain reduction (conditio sine qua non); Improvement of patient's mood or quality of life; A desire expressed by the patient to reduce medication;	No explicit duration Assessment of several outcomes (tolerability, degree of pain relief, etc.). This assessment must take into account the person's disabilities or communication difficulties.

	Belgium	France	The Netherlands	Germany	UK
				A desire of the patient to be implanted	
Patient management	Management by a multidisciplinary team in an approved implanting centre	Management by a multidisciplinary intractable chronic pain team in the context of "pain consultations" A long-term follow-up in the context of "pain consultations"	Management by a multidisciplinary team and in notified centres minimum 20 interventions/year A registration (not mandatory) for quality assessment	Management by a multidisciplinary team + a mandatory certification as pain centre would be desirable in the future A long term follow-up phase / quality assurance phase, including an assessment of safety and effectiveness in the long term	Management by a multidisciplinary team
Reimbursement mechanism	Procedure covered by the DRG system of payment + additional amount for the implant	Procedure covered by the DRG system of payment + additional amount for the implant	Procedure and implant globally covered by the DRG system of payment (specific procedure codes)	Procedure and implant globally covered by the DRG system of payment + supplementary fees (ZE amount)	Volume and price for the implant locally negotiated and the related "DRG" tariff is adapted to ensure that the exclusion of the implant from the "DRG" tariff is cost neutral. The creation of a more specific DRG is in process
Yearly SCS /million	Approx. 84.6 (2009)	Approx. 11.35 (2010)	Approx. 54.3 (2011)	Approx. 11.70 (2010)	Approx 21.5 (Only England estimates, 2010-2011)
Yearly intrathecal delivery pumps /million					
IADP only	Approx 18.3 (2009)	NA	Approx 1.4 (2011)	NA	Approx 1.6 (2010-2011)
IADP + Baclofen	Approx 34.6 (2009)	Approx 1.72 (2010)	Approx 4.5 (2011)	Approx 13.12 (2010)	Approx 9.7 (2010-2011)

NA: Not available – Descriptions are translated from the original language and all numbers are best estimates – Empty boxes do not automatically mean that it is not considered in the country but could also be unavailable information; Implants accepted for reimbursement and coverage

Analysis of the sample of neighbouring countries shows that the reimbursement mechanisms vary:

- In France, the procedure is covered by the "DRG" system of payment and a supplementary amount is reimbursed for the implant. The implant must be included in the limitative list of reimbursed product and services (LPP) and have a LPP tariff for reimbursement otherwise the implant is only partially covered by the procedure
- In the Netherlands, the implant and the procedure are globally covered by the "DRG" system of payment, using specific procedures codes for these implants
- In Germany, the procedure and the implant are covered by the "DRG" system of payment and supplementary fees are given because they are considered as complex and expensive (sometimes on a hospital basis depending of negotiations, e.g. for rechargeable SCS)
- In UK, the volume and price for the implant is locally negotiated and the related "DRG" tariff is adapted to ensure that the exclusion of the implant from the "DRG" tariff is cost neutral. It should be noted that the creation of a more specific DRG is in process

Specific conditions were usually defined for the choice of the implant:

- In France, rechargeable SCS are only specifically covered for:
  - Patients having already had a primo implantation with a non-rechargeable implant and for which the service life was inferior to 30 months or
  - New patients with a stimulation threshold superior to 3.5V at the end of the trial period
- In the Netherlands, the implant choice has to be taken in a recognised "pain" centre trough negotiations between the patient and the multidisciplinary team
- In Germany, supplementary fees for rechargeable SCS were only accorded on a hospital per hospital basis after negotiations between the hospital and the sickness funds
- In UK, the decision is based on the complexity of pain pattern and the stimulation threshold. In case of equally suitable devices, the least costly must be chosen

6.6.2. *Approved indications*

Concerning the indications, SCS is recommended for patients with pain of neuropathic origin in every country. However, the definition of pain of neuropathic origin is not always clear. This definition usually includes pain secondary to FBSS and CRPS, except in Belgium where CRPS is not reimbursed according to an interpretative rule of RIZIV/INAMI. It should also be noted that some countries do not consider pain due to diabetic neuropathy as an indication (France, the Netherlands and Belgium). For ischemic pain, recommendations varied between countries:

- Not recommended in UK
- Only recommended for refractory angina pectoris in the Netherlands
- Only recommended for PAD in France
- Recommended for both refractory angina pectoris and PAD in Germany
- Only recommended in some cases (no clearly defined indications) in Belgium

It should also be noted that chronic pancreatitis and thromboangiitis obliterans seems to be considered as an indication only in Belgium.

- IADP is usually indicated for patients with severe chronic pain refractory to oral drug therapy or with significant side effects of drug therapy

6.6.3. *Prescription and use modalities*

For both SCS and IADP additional requirements are defined, such as failure of other therapeutic measures, a deep assessment of eligibility and a treatment by a multidisciplinary team, the completion of a trial phase (if specified for +/-10 days in the countries we compared, except in Belgium: 4 weeks), and organization of a long-term follow-up and quality insurance.

In some countries, the SCS and IADP implants can only be performed in recognised ("pain") hospitals/centres.

6.6.4. Number of procedures

Even if the quality of these estimates is limited (sometimes based on expert opinions and with a risk of underestimation in some countries), the analysis shows that Belgium is the country with the highest number of procedures. Compared to other countries, the number of procedures in Belgium is between 2 to 7 times higher for SCS and between 3 and 20 times higher for IADP.

6.6.5. Conclusion

Reimbursement conditions defined in other countries could be food for thought in Belgium, with more attention on the covered indications (e.g. coverage for CRPS, diabetic neuropathy, or ischemic pain such as angina pectoris), the duration of the trial phase (<4 weeks?), the assessment and treatment by multidisciplinary teams in a recognised pain hospital/centre, and the number of procedures performed.

6.7. Key points

The Belgian figures for the use of neuromodulation are strikingly higher than in the other four countries.

The specific reimbursement mechanisms vary across countries:

- **Use of a DRG system of payment with specific procedure codes that globally covers the procedure and the implant (the Netherlands)**
- **Use of a DRG system of payment with specific procedure codes that globally covers the procedure and the implant + supplementary fees for their complexities, sometimes based on negotiations (Germany)**
- **Use of a non specific DRG that covers the procedure and use of a limitative list that covers the implant (France)**
- **Use of a non specific DRG that covers the procedure and local negotiations for the implant (NB specific DRG in process) (UK)**

Specific conditions were usually specified for the choice of the implant:

- **Rechargeable SCS only if device service life < 30 months after primo implantation or stimulation threshold > 3.5V at the end of the trial (France)**
- **Decision based on the complexity of pain pattern and the stimulation threshold + the least costly for equally suitable devices (UK)**
- **Negotiation on a hospital-by-hospital basis in contracts between hospitals and sickness funds for rechargeable SCS (Germany)**
- **Choice made by a recognised pain centre in negotiation with the patient (the Netherlands)**

The indications for SCS are:

- **Neuropathic pain secondary to:**
  - **CRPS (in all countries except in Belgium)**
  - **FBSS (in all countries)**
  - **Diabetic neuropathy (only in Germany and in UK);**
  - **Other neuropathic pain (e.g. phantom pain, etc. depending of the country and not always well-defined)**
- **Ischemic pain:**
  - **Refractory angina pectoris (only in the Netherlands and in Germany)**
  - **PAD (only in France, Germany and Belgium in selected cases)**

Specific indications for IADP are:

- **Severe chronic pain refractory to oral drug therapy or with significant side effects**

For both IADP and SCS other requirements include:

- **Failure of other therapeutic measures**
- **Assessment of eligibility and treatment by a multidisciplinary team**
- **Assessment and treatment in a recognised pain centre**
- **Successful completion of a trial phase of variable length**

7. NEUROMODULATION USE IN BELGIUM

7.1. Methodology

For the description and evaluation of neuromodulation use in Belgium we use routinely collected reimbursement and clinical data supplemented with expert opinion. We describe the methodology and the main results only briefly. More details can be found in the appendix.

For the purpose of this evaluation the terms *'implants'* or *'devices'* refers to neurostimulators and drug delivery pumps strictu-sensu, distinguishing them from other accessories such as electrodes, patient programmers, catheters and reservoirs, although strictly speaking all those devices are considered implants in the Belgian regulations.

7.1.1. Description of the Belgian administrative databases used

7.1.1.1. Minimal Hospital Data

The registration of the Minimal Hospital Data (MZG–RHM)[k] is mandatory for every hospital in Belgium since 1991. As a result, for each hospitalised patient, information such as date of birth, gender, postal code of residence and other information such as length of hospital stay, hospital ward and bed type occupation etc., has to be recorded, along with ICD-9-CM encoding of relevant diagnoses as well as diagnostic and therapeutic procedures performed. Diagnosis and procedure codes are collected by attended hospital department, each of those encoding for one primary and several secondary diagnoses. After stripping direct patient-identifying information, records have to be sent twice a year to the federal Ministry of Health (FOD–SPF). At the Ministry, all department registrations are concatenated with assignment of the principal diagnosis of the whole stay, determinant for the APR-DRGs assignment.

7.1.1.2. Hospital and Day Care Billing Data

Since 1995 the Minimal Hospital Data Set records are afterwards linked to the Hospital and Day Care Billing Data (AZV/ADH–SHA/HJA) that are transmitted yearly by the sickness funds (VI – OA) to the National Institute for Health and Disability Insurance (RIZIV–INAMI) and assembled for each hospital stay. The linkage of those registrations is performed by a legally instituted 'Technical Cell' (TCT) and requires separately sent matching tables containing for each identifiable hospital stay a unique patient pseudonym created by two separately executed hashing algorithms. This linkage process takes about 2 years for data assembly, completion and full validation. Successful linkage proportion nowadays exceeds 95% overall, meaning that the relationship between treated pathology and the costs to the health care system can be studied for 'in patient' hospital admissions. The advantage of those coupled data is that registration is compulsory for all regular hospitals (not for private clinics performing e.g. aesthetic surgery) and that claims from all sickness funds are included. Since 2006, those data also contain the one-day hospital stays.

In this report we refer to these coupled databases as the 'Clinical and Billing Data'.

7.1.1.3. RIZIV–INAMI 'N documents'

The so-called N documents are accounting data transmitted each quarter by the sickness funds to the RIZIV–INAMI. They also include the amounts reimbursed by each sickness fund by nomenclature code (mainly medical honoraria and implants; pharmaceuticals are excluded).

7.1.2. Data extraction

For this study, we used data extracted from the Minimal Hospital Data Set (MZG – RHM) between 2002 and 2008 and from the nation-wide billing data from 2002 until 2009. For 2009 clinical data were not available yet at the time of analysis.

[k] We use the recent denomination (before 2008, this database was called RCM/MKG – Résumé Clinique Minimum/Minimale Klinische Gegevens)

The stays were at first extracted if at least one of the RIZIV–INAMI pseudo-codes from the list of neurostimulators (SCS) or IADP material (see Table 71 in the appendix; stimulators, electrodes, pumps or IADP accessories) was registered on the hospital bill and therefore in the billing data. In a second step, next to the originally selected stays (index hospitalizations), we obtained all other hospitalizations from 2002 till 2009 for those patients. It is thus possible to follow a same patient through his/her hospitalizations 2002-2009.

N documents are regularly sent by the actuarial service of the RIZIV–INAMI to subscribers including the Belgian Healthcare Knowledge Centre. The data related to the SCS and IADP pseudo-codes were extracted for 2002-2009.

7.1.3. Analysis

Analyses were performed on the data that were successfully coupled by the TCT after their validation process, discarding stays for which the information of the RHM–MGZ was inconsistent with the billing data.

In a first step, we analysed stays during which a SCS or an IADP was recorded. Characteristics of the patient and the hospital were compared for both therapies, as well as stay characteristics such as diagnoses coded in ICD-9-CM classification. When available the hospital where the procedure was performed was assumed to be location where the patient was treated. When this last information was not available, the hospital of admission was chosen. Mergers of hospitals occurred in this analysed period and the data were transformed to reflect the situation in 2010. As for 2009 no clinical data were available, some analyses could not be run for 2009 because of missing information (such as patients' residence or diagnoses). Wherever possible, we compared 2009 with previous years.

Comparisons of proportions or means between groups were statistically tested with respectively chi-square or t-tests, except when the Q-Q plots showed that the quantitative distribution was not Gaussian (length of stay and costs). In this case, a non parametric test was preferred (Kruskall-Wallis followed, if significant, by pair wise two-sample Mann-Whitney tests using the Bonferroni correction). N documents were used to validate the number of implants found in the Clinical and Billing data.

In a second step, stays from a same patient were all considered as a whole and patient chronology was constructed. Based on the information gathered, the lifetime of the devices was compared in a survival analysis, using the Kaplan-Meier method. Sensitivity analyses were run to compensate the lack of information on mortality outside hospitals (see section 0 for details). Confidence intervals (CI) around the median lifetime are 95% CI.

Finally the total hospitalization costs associated with both therapies were calculated. Since all hospitalizations of the patients selected during the initial selection step were available, it was possible to follow a patient through time until 2009. SCS or IADP implantations were thus identified in 2009 and costs calculation was also possible for 2009.

We first calculated the hospitalization costs of the device implantation hospitalization only. Then, we calculated the whole device implantation episode including the costs of the hospitalizations recorded in the two months preceding the device implantation. This allowed us to capture the four-week trial period including the hospitalizations for electrodes (SCS) or catheter (IADP) implantation. Finally, we examined every hospitalization with admission date in the 2 months previous to implantation including it in the calculation scope only when the procedures performed or the implants invoiced during this hospitalization were related to the device therapy.

Hospitalization costs are defined as all amounts reimbursed by the national healthcare insurance for the procedures (RIZIV – INAMI *'nomenclature'*) performed during the hospital stays, the implanted devices, the pharmaceuticals, the clinical biology examinations, and other products such as blood or radio-isotopes needed during the hospitalization. The hospitalization admission lump sums and per diem lump sums were replaced by the full day prices per bed type published by the RIZIV/INAMI for each hospital multiplied by the number of days spent in the hospital per bed type (see appendix for more explanation on this procedure). Data were cleaned as explained in the appendix prior to the costs calculation. Violin plots are used to depict the costs distribution. Such plots basically combine a classical box plot with the probability density of the data.

Data analysis was performed using SAS 9.2,[152] and R.[153]

7.2. Implanted systems: number, cost and geography

After data reception, we performed data cleaning from which these steps are described in the appendix. Finally, we obtained data for analysis from 3444 SCS implants and 718 IADP implants between 2002 and 2008. For 2009, we collected records on 693 SCS and 156 IADP implants.

The number of constant flow pumps in our IADP data was low: 9 (1.25%) were implanted between 2002 and 2008 and 6 (3.8%) in 2009. Baclofen pumps used in intractable extremity spasticity are not considered in the IADP figures since these are reimbursed under another pseudo-code than IADP. For both techniques figures include primo- and replacement implants.

7.2.1. Under- and over-reporting in the data

In the early phases of analysis we became aware that the SCS numbers in the clinical and billing data set were, on average, 20 to 25 % lower than the actual number of implants reported in other datasets such as the N documents. The reason for this underreporting is technical and due to the design of the data collection model, the main reason being a late billing of the procedures in some cases as explained in more detail in the appendix. This under-reporting occurs theoretically for both SCS and IADP devices.

Before August 1st, 2010, IADP accessories (catheter or personal therapy manager) were reimbursed using the same billing code as the pump itself. Therefore, the number of billed IADP units in the N documents represented an overestimate of approximately 45%. Based on the amounts reimbursed per implant in our data, we were able to differentiate between accessories and pumps and calculate an annual extrapolation factor to estimate the actual number of pumps implanted per year. The same phenomenon was observed in the recording of rechargeable SCS in 2009; for each device, two units were recorded in the N documents, one for the SCS device and one for the charging system. The number of units had therefore to be corrected.

Lastly, data from the one-day hospitalizations are available in the Clinical and Billing Data only from 2006 onwards. We therefore missed some implants between 2002 and 2005, and this happens for both device types.

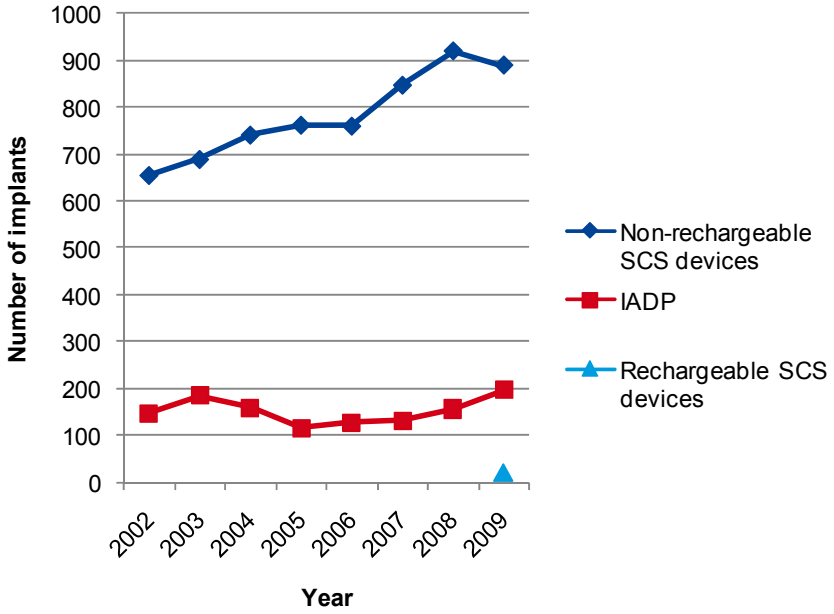
7.2.2. Volumes and device expenses

Taking all these issues into account, the number of implants in 2009 can be estimated at 910 SCS (including 21 rechargeable devices) and 197 IADP. For reference, the number of 'Baclofen pumps' in 2009 was estimated at 174, slightly less than the number of IADP. Details are available per year in the appendix. The evolution of the number of devices is shown in Figure 3. The number of non-rechargeable SCS devices slightly decreased in 2009, probably replaced by the rechargeable type that is reimbursed since the November, 1st of that year. The 2010 figures available in 2012 were still partial and are not depicted in the chart. Nevertheless, we estimated that 553 non-rechargeable SCS, 143 rechargeable SCS and 95 IADP were already registered. This means that around 20.6% of the SCS implanted in 2010 were likely to be rechargeable.

Figure 4 presents the evolution of the RIZIV/INAMI expenses for the material (including device and accessories). For SCS devices, non-rechargeable and rechargeable devices expenses were added to the positive electrodes expenses. The total expenses (SCS and IADP) reached € 10 800 000 in 2009. Negative electrodes expenses (not on the chart), increased from around € 100 000 in 2002 to € 150 000 in 2009.

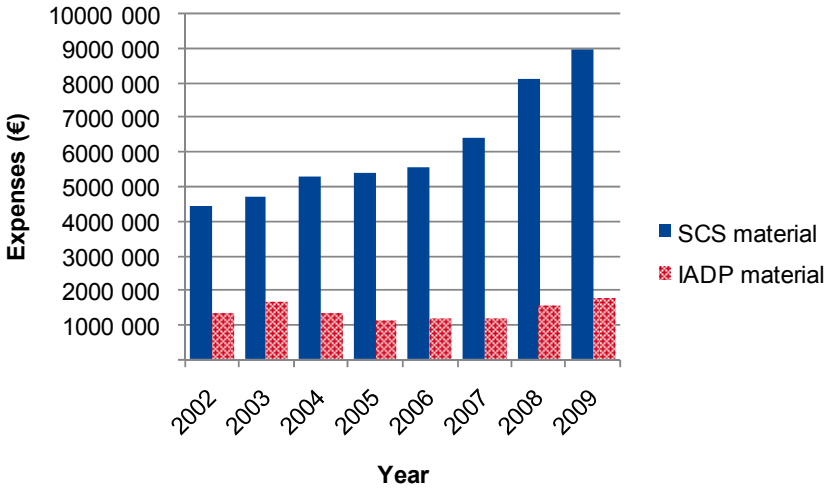
The majority of electrodes become positive electrodes after the four-week trial period. In the year 2009 for example, there were 2048 positive electrodes versus only 117 negative electrodes. This might indicate that more than 90% of SCS trial periods are followed by a final implant. Since the identification of negative trials of IADP catheters in only possible since August 1st 2010, a similar analysis could not be made for IADP.

Figure 3 – Number of SCS and IADP implants in Belgium (2002-2009)



Source: RIZIV–INAMI N documents, Clinical and Billing Data. Rechargeable SCS devices were only reimbursed during the last few months of 2009.

Figure 4 – Total RIZIV–INAMI expenses for the SCS and IADP material (2002-2009)

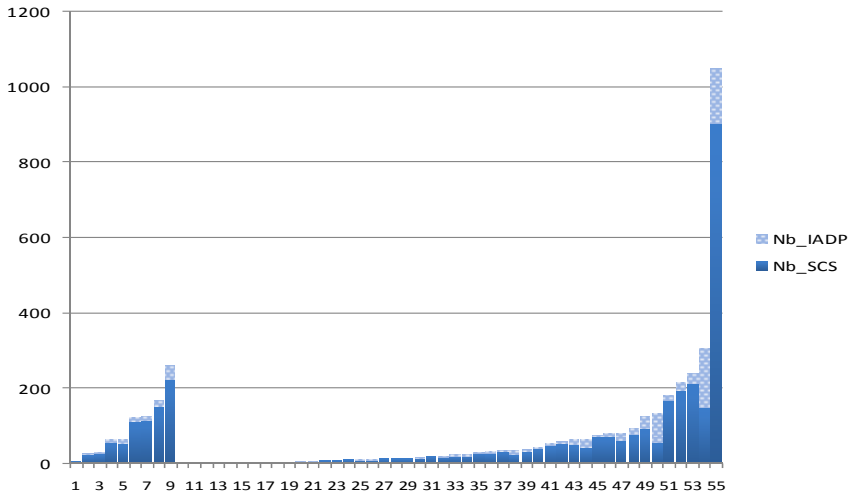


7.2.3. Geography of implants

Figure 5 shows the number of implants in the 55 hospitals where at least one implant was performed between 2002 and 2008 ranked by the total number of implants. The 9 hospitals recognised as referral centres for chronic pain are shown on the left side of the horizontal axis.

Most of the neuromodulation devices were implanted in Oost-Vlaanderen (43% for SCS and 41% for IADP), followed by West-Vlaanderen (14%/30%), Antwerpen (10%/12%) and Limburg (10%/5%). Liège performed 9% of the SCS implantations and 5% of the IADP ones. Brussels implanted only 4% of SCS implants and 2% of IADP. There were only 3 SCS implants in the province of Luxembourg and no IADP. More details can be found in Table 87 and Table 88 in the appendix.

Figure 5 – Number of SCS or IADP implants per hospital (2002-2008)



The centres on the left of the graph are the nine hospitals that are recognised as referral centres for chronic pain as described in chapter 6.

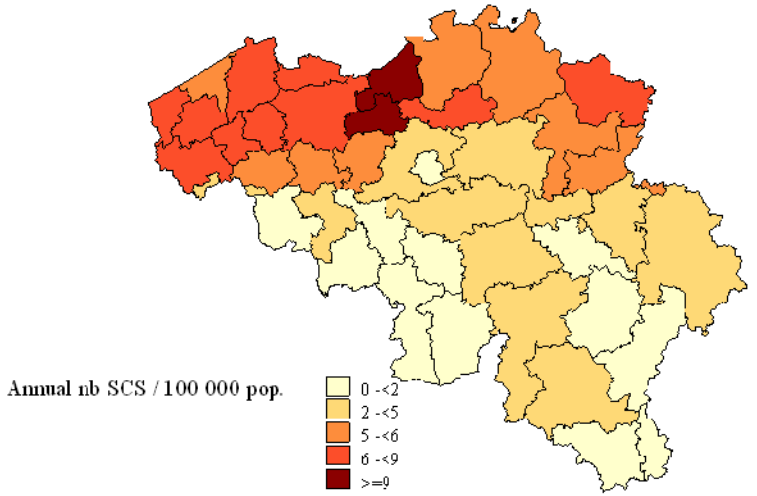
7.2.4. Geography of patients

The majority of the patients also lived (official residence) in Flanders, especially in the provinces of Oost-Vlaanderen and Antwerpen. In absolute numbers patients living in those two provinces accounted for nearly half the implants of neuromodulation devices in Belgium in the period 2002-2008. The incidence by district (arrondissement) of the patient's residence is given in Figure 6 and Figure 7.

In the same analysis period 32 implants were performed on foreigners (only those interventions that were covered by the Belgian health insurance were included), from the Netherlands (27), France (3) and Luxembourg (2); 15 of those implants were performed in West-Vlaanderen and 13 in Oost-Vlaanderen.

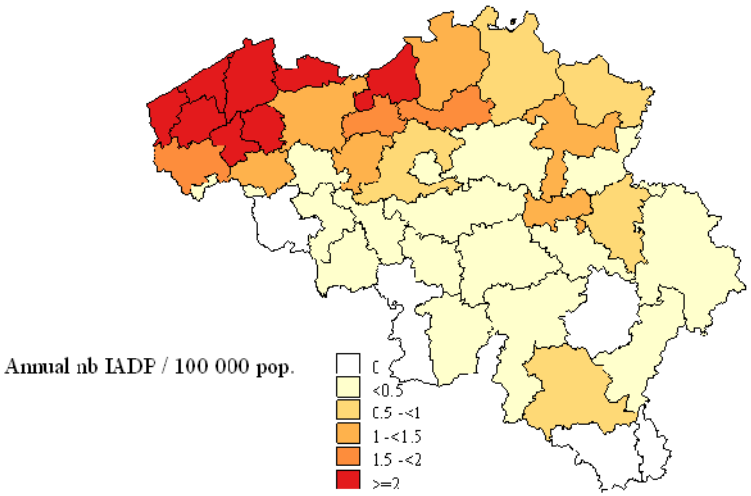
The province and the country of the patient are not available from the billing data 2009 but the ranking by hospital province was roughly similar (see Figure 17 and Table 87-Table 88 in the appendix).

Figure 6 – Number of SCS implants /100 000 inhabitants (residence)



Density of SCS implants by district (arrondissement) in Belgium

Figure 7 – Number of IADP implants /100 000 inhabitants (residence)



Density of IADP implants by district (arrondissement) in Belgium

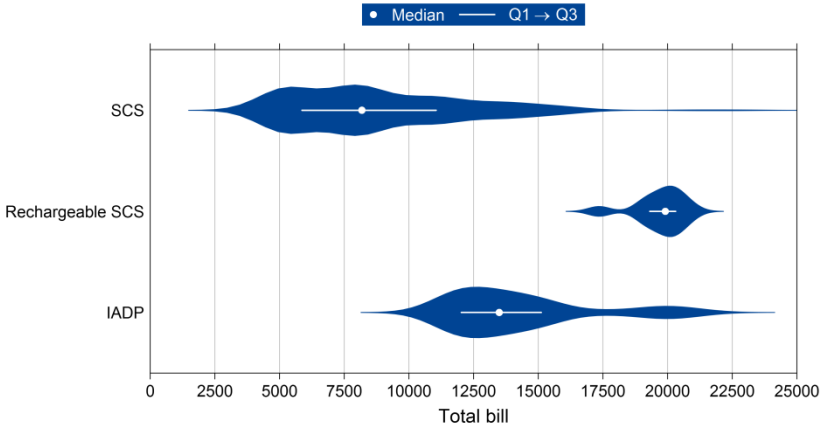
7.2.5. Total hospitalization cost per implant

Three scenarios were chosen to calculate the hospitalization costs. The cheapest one (1) included only the hospitalization during which the device was implanted (index hospitalizations). In the most expensive scenario (3), the hospitalization costs pertained to the whole device implantation episode, including the costs of the hospitalizations recorded in the two months preceding the device implantation date (in order to capture the four-week trial period). The in-between scenario, which is the scenario presented here, consisted in adding only the hospitalizations which were found related to the device therapy to the index hospitalization. The total hospitalization costs calculated so per type of device therapy are presented in Figure 8 for 2009 (non-rechargeable SCS n=251, rechargeable SCS n=10 and IADP n=36). Results for the three scenarios are presented in the appendix.

The most expensive implant therapy, although calculated on a small number of devices, was the rechargeable SCS, with an average total cost of € 19 694 (SD=€ 997, median=€ 19 912), higher than IADP (average € 14 254, SD=€ 2758, median=€ 13 493) and non-rechargeable SCS (average € 8805, SD=€ 3340, median=€ 8184) (Kruskal-Wallis, p<0.0001 – all 3 Mann-Whitney test one-sided p≤0.0001). The material (device and accessories) accounted on average for € 18 507 for rechargeable SCS (SD=€ 717, median=€ 18 596), € 10 107 for IADP (SD=€ 296, median=€ 10 092) and € 7511 for non-rechargeable SCS (SD=€ 2652, median=€ 7095) (same, statistical significance reached than for total bill).

More detailed results can be found in the appendix.

Figure 8 – Total hospitalization costs per type of implants (2009)



Distribution of reimbursements by device type. Median is represented by a dot and the line is delimited by the 1st and 3rd quartile estimates using a Gaussian kernel function

On average, the amount reimbursed for the implants (including device and accessories) represented 94% of the total bill in case of rechargeable SCS therapy, 85.3% in case of other SCS therapy and 70.9% in case of IADP therapy. The reimbursement of the implanted material in itself is thus the largest cost driver. The IADP cost also more than the SCS therapy because the length of the stay during which the device was implanted was longer: 5.4 days on average (SD=3.6, median=4.5) versus 1.4 (SD=2.3, median=1) for SCS and for rechargeable SCS. All comparison tests were statistically significant (p≤0.0001) except that SCS and rechargeable SCS had no difference in length of stay (Mann-Whitney test, two-sided p=0.74). None of the IADP was implanted in one-day stay unlike most of the SCS devices (140/251=56%). Three out of the ten rechargeable SCS were implanted in one-day.

7.2.6. Yearly cost of neuromodulation implants in Belgium

Estimating the total costs of neuromodulation in Belgium for the year 2009 is hampered by several potential biases. According to our three cost scenarios including hospital costs, and using our estimates for the total number of implants, the 2009 total costs for the neuromodulation (excluding negative electrodes) would range from € 10.8 million to € 11.7 million. However, in the same year 2009, the RIZIV – INAMI reimbursement cost for neuromodulation material alone was € 10.8 million. Independent of the scenario chosen the hospitalization costs calculation per patient were therefore probably lower than the reality and some costs might have been missed.

Several technical reasons may explain these differences. First, we selected on device implants, but material like electrodes or catheters could be replaced outside the 2 month period preceding the device implant itself, due to malfunction or migration. This material would not be included in our costs estimates but it is in the RIZIV – INAMI total budget of neuromodulation device material. Second, atypical and therefore more expensive patients were discarded from our estimates because we tried to describe costs for an *'average'* patient. This was done for patients receiving more than one device during the same stay or with devices implanted during consecutive stays. However, patients receiving a device with no reimbursement (device offered by the manufacturer within a warranty period) were not included in the estimate. Finally, a selection bias may have been introduced by discarding patients during the coupling process of the databases. The direction of the latter bias cannot be determined but this could be associated with patients in whom billing was more complicated and therefore delayed and not included in our database.

Based on the real 2009 neuromodulation material reimbursement and knowing that approximately 85% of the global costs represent material costs the 2009 global budget for neuromodulation implants can be estimated to be approximately € 12.5 million.

7.3. Patient characteristics

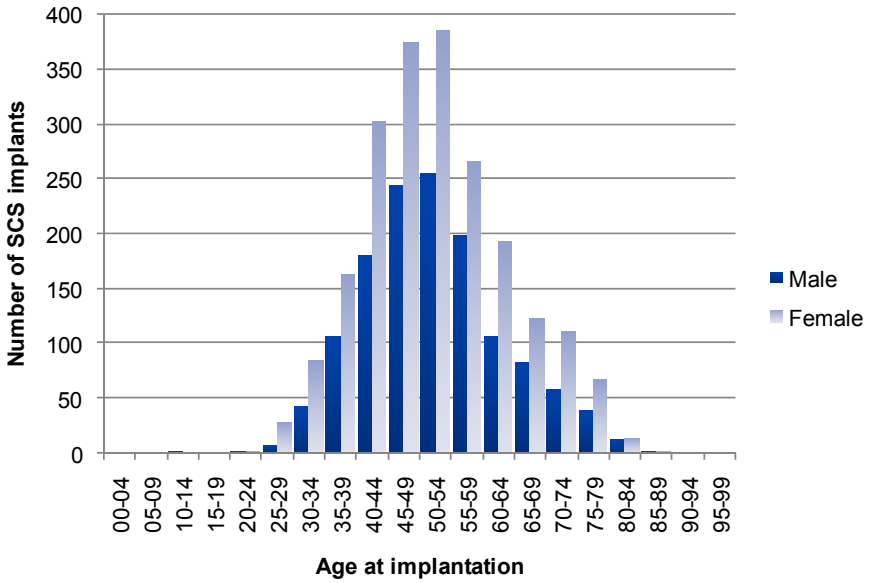
7.3.1. Age and gender

Figure 9 shows the patient age distribution by gender and for SCS and IADP separately. Some patients were implanted more than once (2876 patients accounted for the 3444 SCS implants and 698 patients for 718 IADP implants). The age of the population receiving a SCS was on average 51.9 years (SD: 11.4) versus 54.8 years (SD: 12.1) for the patients receiving an IADP (t-test p<0.0001). The gender proportion was similar in both groups, showing that about 60% of patients were female (chi-square, p=0.105). More detailed data can be found in Table 77 and Table 78 in the appendix.

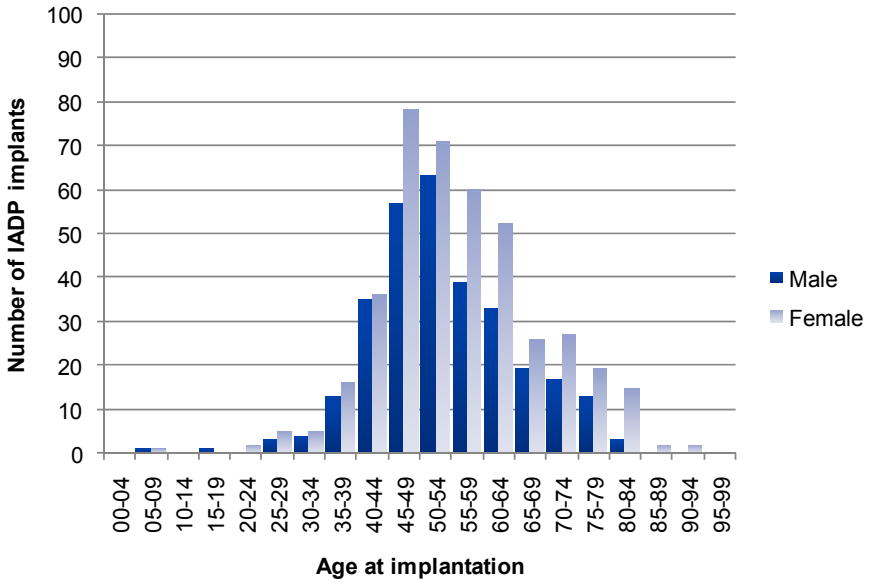
In 2009, the age was on average 53.6 years (SD: 11.2) at SCS implantation and 56.9 years (SD: 10.2) at IADP implantation (t-test, p=0.0007), which was not significantly older than 2002-2008 (one-tail test, p=0.39). Also the proportion of women, 60.9% (SCS) and 67% (IADP), did not differ significantly.

Figure 9 – Age and gender distribution (2002-2008)

SCS



IADP



7.3.2. Chronology of implants

Table 89 in the appendix gives the detailed number of implants by patient. The 4162 SCS or IADP implants were distributed between 3467 patients. Eighty-five percent of the patients had only 1 implantation selected between the first of January 2002 and the 31st December 2008. One patient had up to 9 selected implants recorded during that period. As the 2009 data are not coupled with the MZG–RHM, the 2009 patients cannot be related to the 2002-2008 patients.

The combinations found in our data are shown on Table 90. Besides the delayed reporting as explained in 7.2.1, two other possible biases (underestimations) must be kept in mind. First, the first implantation may follow other implants performed before 2002 and second, one-day hospitalizations are only included in the data from 2006.

7.3.3. Hospital diagnoses

The most frequent principal diagnoses that are encoded amongst the clinical data are similar for SCS and IADP patients, as shown in Table 12. This top-5 of principal diagnosis accounts for over 80% of all principal diagnosis during implants of neuromodulation systems.

The most frequent principal diagnosis recorded is the non-specific V53 'Fitting and adjustment of other device'. Together with the two other non-specific diagnoses in this top-5 list (724 and 996) these codes account for almost 60% of all principal diagnosis codes.

This was a disappointing result since we had hoped to use this diagnostic information to further enlighten us on the patient case mix and indication setting applied in Belgian hospitals.

The most frequently recorded specific principal diagnosis was ICD 722.8x, postlaminectomy syndrome (14.7% of all principal diagnoses with SCS and 17.1% for IADP). Excluding the unspecified region codes (~25%) the lumbar region accounted for more than 80% of the postlaminectomy syndrome regions.

Other diagnosis codes encountered were difficult to interpret accurately. More detailed information on these diagnostic data can be found in Table 79 to Table 86 in the appendix.

Table 12 – Age and gender of patients with one of the Top 5 Principal diagnoses in 3 digits (2002-2008) for 3444 SCS and 718 IADP implants

PRINCIPAL DIAGNOSIS		SCS implantations				IADP implantations			
		N	Female %	Age Mean	Age Std	N	Female %	Age Mean	Age Std
V53	Fitting and adjustment of other device	1135	63.3%	52.7	10.2	162	59.9%	55.9	11.8
722	Intervertebral disc disorders	656	60.1%	50.7	11.7	159	61.0%	54.2	12.1
724	Other and unspecified disorders of back	487	61.8%	50.9	12.1	128	61.7%	54.6	11.2
996	Complications peculiar to certain specified procedures	339	61.1%	51.7	10.9	127	47.2%	55.8	11.2
355	Mononeuritis of lower limb	183	56.3%	53.0	12.9				
721	Spondylosis and allied disorders					21	61.9%	58.8	11.6

7.4. Indications in practice

7.4.1. Expert opinion

During this project expert opinion was gathered from clinicians and reimbursement officials to quantify the indications for the use of neuromodulation in Belgium.

Although this information was mainly anecdotic in nature a few general conclusions prevail:

- The main indication for neuromodulation (especially SCS) is FBSS;
- Estimated proportions for FBSS as indication vary but go up to 80% of all neuromodulation interventions
- There is a general feeling among experts that back surgery is performed more frequently in Belgium compared to surrounding countries
- IADP is perceived by many experts as used only as a therapy of last resort, when no other options remains available
- In practice IADP is used for treating cancer pain although it is not an explicitally approved indication
- On average, patients are described as being generally middle-aged but with a reasonable life expectancy

7.4.2. Data analysis

Since it is believed by experts that in practice the main indication for neuromodulation in Belgium is FBSS we wanted to corroborate this expert opinion using the hospital clinical data set recordings.

As shown in section 7.3.2 the ICD diagnosis codes for patients receiving an implant were in general rather unspecific. As a result the information on specific indication from the routinely registered Belgian minimal clinical data set data through the reimbursement system was rather disappointing regarding information on specific indications.

As shown in section 7.3.3 we found in only 14 to 17% of neuromodulation implants a diagnosis code corresponding to postlaminectomy syndrome, with approximately 80% located in the lumbar region.

However, since we also collected the information about all hospital stays in the period 2002-2008 we were able to document *'back surgery'* preceding implants of neuromodulation systems in a limited period of five years. To identify patients with a potential indication of FBSS we selected those patients, for whom at least five year follow-up was available, i.e. neuromodulation during the years 2007 and 2008.

There were 1051 patients who had an SCS or an IADP system implanted in 2007 or 2008 with no other such implant in the period 2002-2008.

Among those patients 32% and 16%, SCS and IADP respectively, underwent back surgery in the five years preceding the implant.

Although those proportions are lower than expected a priori, back surgery might have occurred before this period of 5 years before the implant of a neuromodulation system.

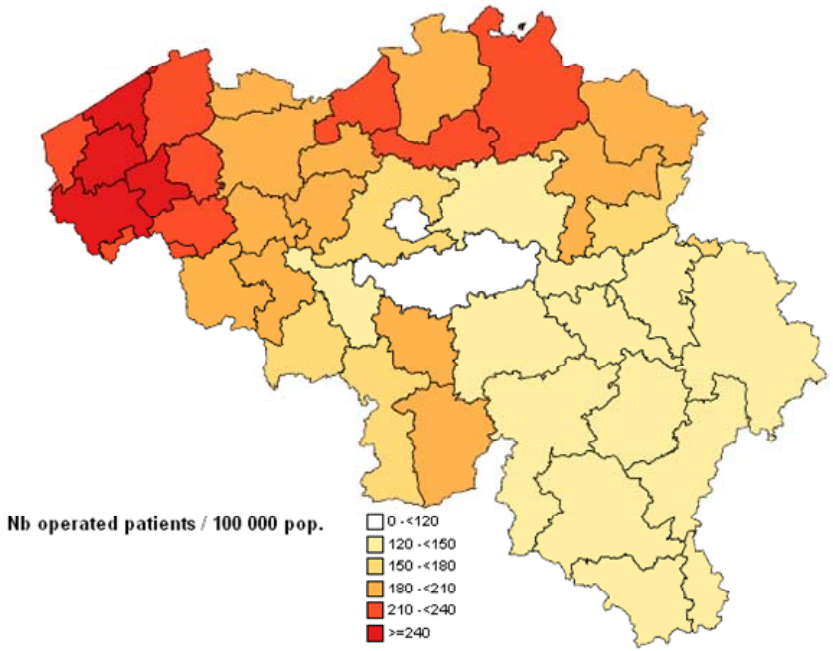
7.4.3. Back surgery in Belgium

It has been reported previously that back surgery is performed more frequently in Belgium. Historical data show that the frequency of surgery for the treatment of low back pain is much higher in Belgium than it is in the Netherlands.[154] Those data show that surgical treatment of low back pain with and without arthrodesis was 4.5 times more common in Belgium compared with the Netherlands.

In 2006 KCE published a report that illustrated this high contribution of surgery in the total cost of treating low back pain treatment in Belgium.[102] This report also demonstrated a regional variation that is remarkably similar to the distribution of the use of neuromodulation in Belgium described in 7.2.4., corresponding to a much higher incidence of both back surgery and the use of neuromodulation in the north of the country An additional analysis of our data from 2002 to 2008 show a similar picture illustrated in Figure 10.

Although the assertion that this high frequency of back surgery causes a higher level of neuromodulation use in Belgium is plausible, it could not be substantiated during this analysis because of a lack of sufficiently good quality data from the minimal clinical data set.

Figure 10 – Yearly incidence of back surgery in patients / 100 000 inhabitants (residence)



Density of back surgery by district (arrondissement) in Belgium

7.5. Device survival

7.5.1. Data and methods

The aim of this survival analysis was to estimate the lifetime of a device (either SCS or IADP) in a real world Belgian context. The Kaplan-Meier method was used.

There is a distinction between the primo-implantation and replacement pseudo-codes in the SCS material when used for inoperable chronic lower limb ischemia but this code was not always used correctly in practice. Moreover, such distinction does not exist neither for any other indication for SCS nor for IADP. Therefore, we identified the replacements by comparing implants to previous implants.

Data were available on all hospital stays during 7 consecutive years (between the beginning of 2002 and the end of 2008) of the patients who had at least one SCS or IADP implanted during these years. However, data on one-day hospital stays were only available since 2006.

An **event** (replacement) was defined as the registered implantation of a device preceded by a registered implantation of the same type of device previously (i.e. again SCS or again IADP) without the implantation of the other device type in between.

Censoring in the ***first analysis*** was defined as the date of:

- SCS implantation followed by an IADP implant or vice versa
- last hospital or one-day discharge of the patient

The date of last hospital or one-day discharge was chosen because no vital parameters were available in this dataset and the date of last discharge therefore provided a proxy for the last known date of being alive.

To evaluate the robustness of the results for this choice we also analysed three alternative scenarios where three different censoring dates were chosen. The same four analyses were run again on the dataset, but limited to 2006-2008 to evaluate the impact of not including the day care hospitalizations in the period before 2006.

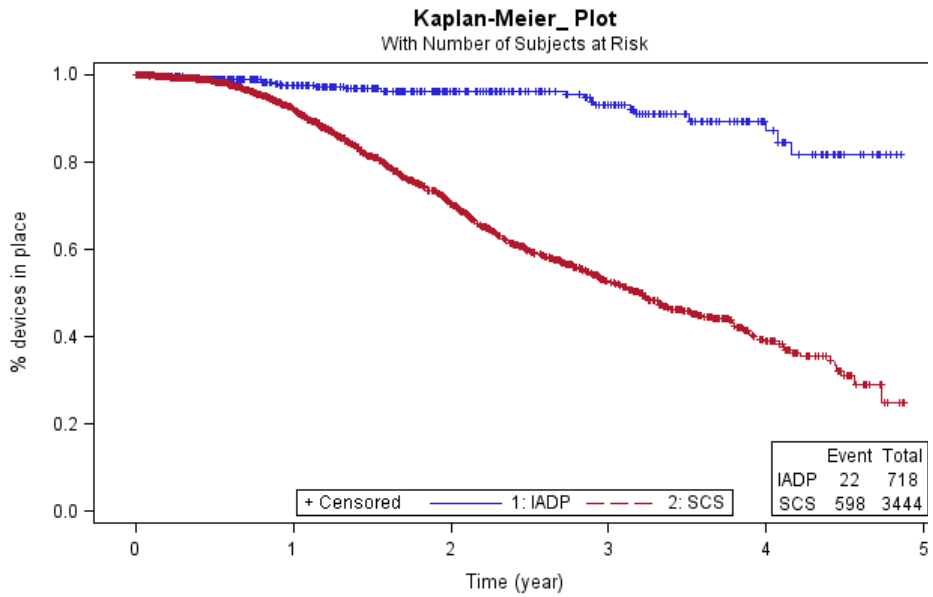
An overview of these eight scenarios is shown in Table 13.

Table 13 – Scenarios for survival analysis

Analysis	Censoring dates			Period
	Other device type Implantation	Last date of discharge	Dec 31, 2008	
Base case	**X**	**X**		2002-2008
2		**X**		2002-2008
3	**X**	**When died**	**When last discharged alive**	2002-2008
4		**When died**	**When last discharged alive**	2002-2008
5	**X**	**X**		2006-2008
6		**X**		2006-2008
7	**X**	**When died**	**When last discharged alive**	2006-2008
8		**When died**	**When last discharged alive**	2006-2008

7.5.2. Analysis 1: Base case scenario 2002-2008

Figure 11 – Device longevity after implantation (2002-2008), base case scenario



The median time to SCS replacement in this analysis scenario was reached at 3.20 years (CI: 2.97-3.39), while the median time to IADP replacement was not observed during this follow-up but was clearly above 5 years. Replacement rates for the five time intervals were also calculated as person-years, as presented in Table 15. The first annual rate is very close to the rate at 1 year (in Table 14).

Table 14 – Replacement rate (Base case scenario 2002-2008)

Device type	Nb implantations	Replaced	Censored	Percent Censored	Replacement rate at 1 year	at 2 years	at 3 years	at 4 years
SCS	3444	598	2846	82.64	8.03	29.55	47.43	61.09
IADP	718	22	696	96.94	2.42	3.64	7.03	12.88
Total	**4162**	**620**	**3542**	**85.10**				

Table 15 – Replacement rate per 100 person-years (Base case scenario 2002-2008)

	SCS					IADP				
Time Interval	Number Interval	Number Censored	Number Failed	Person-Years	Event Rate (%)	Number Interval	Number Censored	Number Failed	Person-Years	Event Rate (%)
[0,1)	3444	1939	137	1829.01	7.49	718	426	9	389.25	2.31
[1,2)	1368	436	261	998.10	26.15	283	119	3	219.73	1.37
[2,3)	671	243	139	462.20	30.07	161	58	4	131.07	3.05
[3,4)	289	166	50	175.52	28.49	99	58	4	65.44	6.11
[4,5)	73	62	11	26.36	41.73	37	35	2	14.74	13.57
Overall	**5845**	**2846**	**598**	**3491.19**	**17.13**	**1298**	**696**	**22**	**820.22**	**2.68**

[0, 1) means that the time interval includes 0 but excludes 1.

7.5.3. Analysis 2: Scenario with censoring only at date of last discharge 2002-2008

Censoring was applied at last discharge only and the implant of another type of device (IADP after SCS or vice-versa) was not considered to be censoring

Figure 12 – Device longevity after implantation (2002-2008), scenario 2

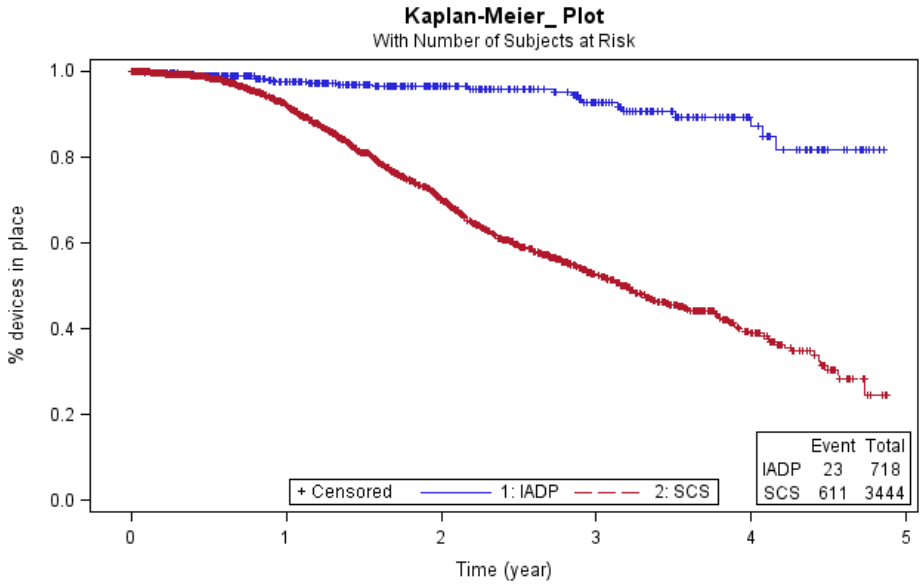


Table 16 – Replacement rate (scenario 2, 2002-2008)

Device type	Nb implantations	Replaced	Censored	Percent Censored	Replacement rate at 1 year	at 2 years	at 3 years	at 4 years
SCS	3444	611	2833	82.26	8.05	29.98	47.66	61.13
IADP	718	23	395	96.80	2.37	3.55	7.31	12.86
Total	**4162**	**634**	**3228**	**84.77**				

The median time to SCS replacement was reached at 3.19 years (CI: 2.94-3.38), while the median time to IADP replacement was not observed during this follow-up but was clearly above 5 years.

Table 17 – Replacement rate par 100 person-years (scenario 2, 2002-2008)

	SCS					IADP				
Time Interval	Interval	Censored	Failed	Years	Rate (%)	Interval	Censored	Failed	Years	Rate (%)
[0,1)	3444	1925	138	1834.46	7.52	718	416	9	395.39	2.28
[1,2)	1381	429	270	1010.33	26.72	293	121	3	228.30	1.31
[2,3)	682	247	141	471.06	29.93	169	59	5	139.11	3.59
[3,4)	294	170	50	177.67	28.14	105	63	4	69.10	5.79
[4,5)	74	62	12	26.62	45.08	38	36	2	15.47	12.92
Overall	**5875**	**2833**	**611**	**3520.14**	**17.36**	**1323**	**695**	**23**	**847.37**	**2.71**

[0, 1) means that the time interval includes 0 but excludes 1.

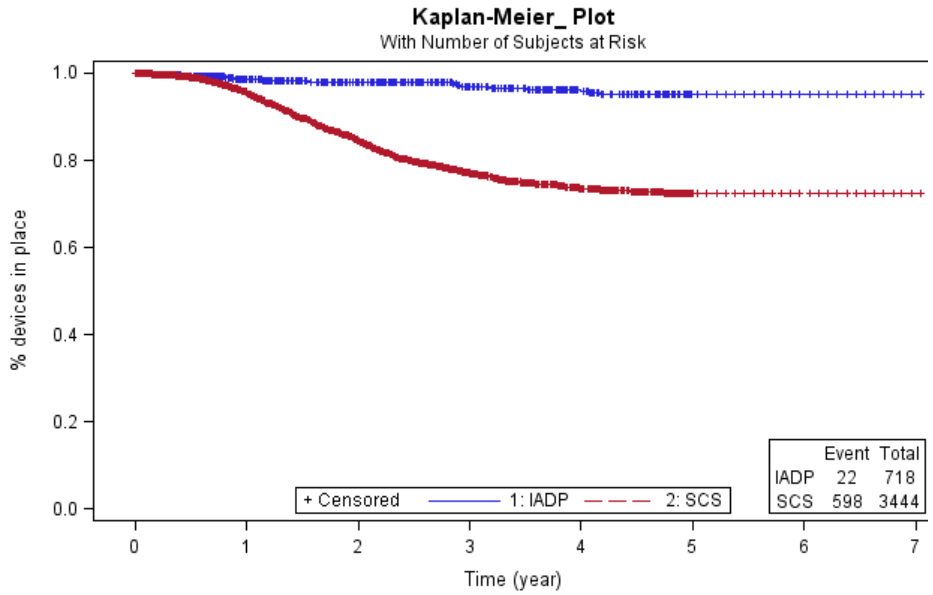
7.5.4. Analysis 3: Scenario with censoring only at end of follow-up period if no dead was recorded previously 2002-2008

Similar as in analysis 1, the implant of another type of device (IADP after SCS or vice-versa) was considered to be censoring.

But, a time-based bias might be possible, caused by patients returning many times to the hospital. The patients had more chance of being observed for a longer time than patients with only few, or no hospital stays.

Therefore, an extremely optimistic sensitivity analysis was made to correct for too early censoring. In this third analysis the patient was not censored at the time of last hospitals stay (unless he/she died in hospital). Device longevity was thus extended to the maximum possible device lifetime (until Dec 31, 2008).

Figure 13 – Device lifetime after implantation (2002-2008), scenario 3



In this optimistic scenario no median time was reached at the end of the observation period for neither device.

Table 18 – Replacement rate (scenario 3, 2002-2008)

Device type	Nb implantations	Replaced	Censored	Percent Censored	Replacement rate at 1 year	at 2 years	at 3 years	at 4 years
SCS	3444	598	2846	82.64	4.63	15.50	22.97	26.44
IADP	718	22	696	96.94	1.40	1.96	2.96	4.13
Total	**4162**	**620**	**3542**	**85.10**				

Table 19 – Replacement rate per 100 person-years (scenario 3, 2002-2008)

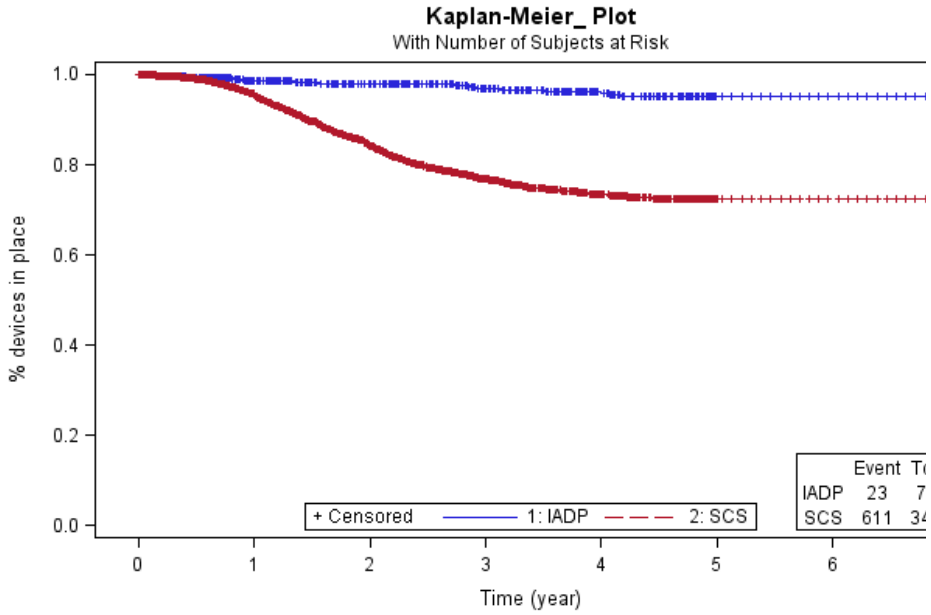
	SCS					IADP				
Time Interval	Interval	Censored	Failed	Years	Rate (%)	Interval	Censored	Failed	Years	Rate (%)
[0,1)	3444	722	137	3070.37	4.46	718	143	9	648.40	1.39
[1,2)	2585	584	261	2155.72	12.11	566	103	3	510.04	0.59
[2,3)	1740	375	139	1466.13	9.48	460	88	4	419.15	0.95
[3,4)	1226	285	50	1064.28	4.70	368	80	4	329.94	1.21
[4,5)	891	247	11	765.79	1.44	284	82	2	247.49	0.81
[5,6)	633	327	0	488.51	0	200	110	0	152.78	0
[6,7)	306	305	0	168.70	0	90	89	0	48.53	0
[7,8)	1	1	0	0.04	0	1	1	0	0.04	0
Overall	**10826**	**2846**	**598**	**9179.54**	**6.51**	**2687**	**696**	**22**	**2356.37**	**0.93**

[0, 1) means that the time interval includes 0 but excludes 1.

7.5.5. Analysis 4: Scenario as in analysis 3 but without censoring at date of implantation of another type of device 2002-2008

Censoring date in this analysis was defined as the date of last hospital or one-day discharge of the patient in case of death or Dec 31st 2008 if the patient was discharged alive. Again this is an extremely optimistic sensitivity analysis.

Figure 14 – Device lifetime after implantation (2002-2008), scenario 4



Also in this second optimistic scenario no median time was reached at the end of the observation period for neither device.

Table 20 – Replacement rate (scenario 4, 2002-2008)

Device type	Nb implantations	Replaced	Censored	Percent Censored	Replacement rate at 1 year	at 2 years	at 3 years	at 4 years
SCS	3444	611	2833	82.26	4.64	15.79	23.24	26.66
IADP	718	23	395	96.80	1.37	1.91	3.08	4.2
Total	**4162**	**634**	**3228**	**84.77**				

Table 21 – Replacement rate par 100 person-years (scenario 4 2002-2008)

Time Interval	SCS Number Interval	SCS Number Censored	SCS Number Failed	SCS Person-Years	SCS Event Rate (%)	IADP Number Interval	IADP Number Censored	IADP Number Failed	IADP Person-Years	IADP Event Rate (%)
[0,1)	3444	703	138	3078.28	4.48	718	126	9	658.24	1.37
[1,2)	2603	577	270	2173.97	12.42	583	101	3	530.00	0.57
[2,3)	1756	374	141	1483.94	9.50	479	90	5	436.37	1.15
[3,4)	1241	291	50	1077.05	4.64	384	84	4	344.19	1.16
[4,5)	900	251	12	772.44	1.55	296	89	2	255.09	0.78
[5,6)	637	330	0	491.64	0	205	111	0	156.99	0
[6,7)	307	306	0	168.91	0	94	93	0	50.63	0
[7,8)	1	1	0	0.04	0	1	1	0	0.04	0
Overall	**10889**	**2833**	**611**	**9246.29**	**6.61**	**2760**	**695**	**23**	**2431.55**	**0.95**

[0, 1) means that the time interval includes 0 but excludes 1.

7.5.6. Analyses 5 to 8 (2006-2008)

There is no registration of one-day hospitalizations before 2006. To evaluate the impact of this lack of information on device survival we re-run the four previous analyses but limited to the period 2006-2008, to homogeneously take into account the registration of one-day hospitalizations from 2006 onward.

These analyses basically show a similar difference between SCS and IADP as in the first four analyses. See Figure 18 in the appendix for more details. Nonetheless, the median lifetime of a neurostimulator in scenarios 5 and 6 is lower than in scenarios 1 and 2: 2.3 years versus 3.2 years. Replacement rates at 2 years for SCS as well as IADP are also higher when calculated on 2006-2008.

7.6. Discussion

This historical dataset of routinely obtained administrative health data covering 8 years of neuromodulation device implants in Belgium showed some remarkable results.

After correcting for various reasons for over- and underreporting the yearly number of implants of IADP devices appeared relatively stable at close to 200 per year while the yearly number of SCS implants increased from around 650 in 2002 to approximately 900 in 2009.

Patients receiving SCS implants were slightly younger than those receiving IADP implants (average 51.9 vs 54.8 years) but the gender proportion was similar with about 60% of them being female. The clinical information from the minimal clinical dataset was disappointing since the ICD codes used were to a large extent unspecific. Therefore this diagnostic information was less relevant than expected.

The distribution of implant centres shows some remarkable differences between hospitals and regions. The majority of implants are performed outside the 9 recognised referral centres for chronic pain and occur mainly in the north of the country. Even more remarkable is that over 25% of all implants are performed in one single centre.

The regional distribution of implants does not seem to be related to the existence of specific referral centres serving the whole country since there is a clear association with the patient origin; nearly half of all patients reside in the provinces of Antwerpen and Oost-Vlaanderen. This might be an indicator of either supply-induced demand or under-use in other areas of the country.

Device longevity can be important, both for patient comfort (avoiding the burden of re-intervention) as for costs (implant and hospital stay). The survival analysis showed a huge difference in device longevity between SCS and IADP devices with an average device lifetime of 3.2 years for non-rechargeable SCS devices in the base case scenario, while the average lifetime was not reached for IADP devices during the 7 years of observation. Likewise the replacement rates at years 1 to 4 were much higher for SCS devices: SCS replacement after 2 year was nearly 30% while for IADP this was slightly lower than 4%. Therefore a choice for rechargeable SCS devices as primo-implantation might make sense, if a short battery life can be predicted. However, the lifetime for rechargeable SCS devices could not be evaluated in this analysis as they were not yet included in this historical database.

The sensitivity analyses show a shorter lifetime of both devices when calculated on the period 2006-2008 only. Two assumptions are possible. First, the lack of one day hospitalizations before 2006 led to an underestimation of the number of replacements. Nevertheless, this explanation is probably true for SCS but is not realistic in the case of IADP (there are less than 5 one-day IADP implantations per year). Second, SCS and IADP are faster replaced recently than in the previous years.

The evaluation of the cost of implantation was hampered by the trial period for neuromodulation devices. As a result of this trial period the cost of implant is spread over at least two hospital stays, one for the implant of the electrode/catheter and another at least four weeks later for the implant of the neuromodulation device. Since the dates in the Clinical and Billing data were not always easy to interpret, we ran 3 scenarios including, in the most expensive option, all hospital costs in the 2 months preceding the implant strictu sensu. The second option, including only the hospitalizations in the two months and directly related to the device therapy, was chosen for its more robust methodology. But conclusions did not differ from the 2 other scenarios. The total cost of implant is highest for the rechargeable SCS device, followed by IADP and the classic SCS. However, the bulk of this cost (70 – 95%) is device related.

Although the use of national administrative data is convenient and available at relatively low cost, some limitations are inherent to routinely collected administrative databases. Their purpose is a priori not scientific; data are collected from a hospital financing perspective. The quality of hospital coding behaviour directly influences the quality of the analyses.

7.7. Key points

Number of devices implanted in Belgium

- In 2009, almost 900 non-rechargeable SCS devices and almost 200 IADP were implanted in Belgium
- Around 20 rechargeable SCS devices (reimbursed only since November 2009) were implanted in 2009 but already more than 140 rechargeable SCS were registered for 2010, which represent 20.6% of all SCS devices

Patient characteristics

- Around 60% of the patients are women
- Patients receiving a SCS were on average slightly younger that those receiving an IADP (52 versus 55 year)
- Most of the registered principal diagnoses of the implantation hospitalization stay were too unspecific for further analysis

Hospital characteristics

- Most SCS implants were performed in West-Vlaanderen, Oost-Vlaanderen and Antwerpen. The same is observed for IADP implants. The majority of patients also lived in those provinces
- Hospitals with the higher number SCS and/or IADP implants were not necessarily Belgian referral centres for chronic pain
- One hospital implanted more than a quarter of all devices

Indications

- The main indication for using neuromodulation (mainly SCS) in Belgium is reported to be FBSS
- IADP is mainly considered as an intervention for patients with no other treatment options left

Device survival analysis

- Median replacement time of SCS devices was 3.2 years, while the median time for IADP was not reached during the follow-up

Hospitalization costs

- On average, the whole hospitalization episode for the device implantation, including the trial, costs almost € 9 000 for the non-rechargeable SCS, € 14 000 for the IADP and € 20 000 for the rechargeable SCS
- The costs of the material (device and accessories) represent the highest cost driver of the whole hospitalization episode costs
- Beside the material, the difference in costs between SCS devices and IADP can also be explained by the longest stay at the hospital for the IADP implantation. SCS devices are mostly implanted in one-day clinic

APPENDICES

1. APPENDIX TO CHAPTER ON CHRONIC PAIN

1.1. Overview of IASP pain definitions

Allodynia

Pain due to a stimulus that does not normally provoke pain. The stimulus leads to an unexpectedly painful response. This is a clinical term that does not imply a mechanism. Allodynia may be seen after different types of somatosensory stimuli applied to many different tissues (also see Table 22).

Analgesia

Absence of pain in response to stimulation which would normally be painful. As with allodynia, the stimulus is defined by its usual subjective effects.

Anesthesia dolorosa

Pain in an area or region which is anesthetic.

Causalgia

A syndrome of sustained burning pain, allodynia, and hyperpathia after a traumatic nerve lesion, often combined with vasomotor and sudomotor dysfunction and later trophic changes.

Central pain

Pain initiated or caused by a primary lesion or dysfunction in the central nervous system.

Dysesthesia

An unpleasant abnormal sensation, whether spontaneous or evoked. Special cases of dysesthesia include hyperalgesia and allodynia. A dysesthesia should always be unpleasant and a paresthesia should not be unpleasant, although it is recognised that the borderline may present some difficulties when it comes to deciding as to whether a sensation is pleasant or unpleasant. It should always be specified whether the sensations are spontaneous or evoked.

Hyperalgesia

Increased pain from a stimulus that normally provokes pain. Hyperalgesia reflects increased pain on suprathreshold stimulation. This is a clinical term that does not imply a mechanism. For pain evoked by stimuli that usually are not painful, the term *allodynia* is preferred, while *hyperalgesia* is more appropriately used for cases with an increased response at a normal threshold, or at an increased threshold, e.g., in patients with neuropathy (also see Table 22).

Hyperesthesia

Increased sensitivity to stimulation, excluding the special senses. The stimulus and locus should be specified. *Hyperesthesia* may refer to various modes of cutaneous sensibility including touch and thermal sensation without pain, as well as to pain. The word is used to indicate both diminished threshold to any stimulus and an increased response to stimuli that are normally recognised.

Hyperpathia

A painful syndrome characterised by an abnormally painful reaction to a stimulus, especially a repetitive stimulus, as well as an increased threshold. It may occur with allodynia, hyperesthesia, hyperalgesia, or dysesthesia (also see Table 22).

Hypoalgesia

Diminished pain in response to a normally painful stimulus (also see Table 22).

Table 22— Overview of some deviant pain definitions as defined above

Allodynia	lowered threshold	stimulus and response mode differ
Hyperalgesia	increased response	stimulus and response mode are the same
Hyperpathia	raised threshold: increased response	stimulus and response mode may be the same or different
Hypoalgesia	raised threshold: lowered response	stimulus and response mode are the same

The above essentials of the definitions do not have to be symmetrical and are not symmetrical at present. Lowered threshold may occur with allodynia but is not required. Also, there is no category for lowered threshold and lowered response if it ever occurs.

Hypoesthesia

Decreased sensitivity to stimulation, excluding the special senses. Stimulation and locus are to be specified.

Neuralgia

Pain in the distribution of a nerve or nerves. This term is common usage, especially in Europe and often implies a paroxysmal quality, but neuralgia should not be reserved for paroxysmal pains.

Neuritis

Inflammation of a nerve or nerves, but should not be used unless inflammation is thought to be present.

Neuropathic pain

Pain caused by a lesion or disease of the somatosensory nervous system. It is a clinical description which requires a demonstrable lesion or a disease that satisfies established neurological diagnostic criteria. The term *lesion* is commonly used when diagnostic investigations (e.g. imaging, neurophysiology, biopsies, lab tests) reveal an abnormality or when there was obvious trauma. The term *disease* is commonly used when the underlying cause of the lesion is known (e.g. stroke, vasculitis, diabetes mellitus, genetic abnormality). *Somatosensory* refers to information about the body per se including visceral organs, rather than information about the external world (e.g., vision, hearing, or olfaction). The presence of symptoms or signs (e.g., touch-evoked pain) alone does not justify the use of the term *neuropathic*. Some disease entities, such as trigeminal neuralgia, are currently defined by their clinical presentation rather than by objective diagnostic testing. Other diagnoses such as postherpetic neuralgia are normally based upon the history. It is common when investigating neuropathic pain that diagnostic testing may yield inconclusive or even inconsistent data. In such instances, clinical judgment is required to reduce the totality of findings in a patient into one putative diagnosis or concise group of diagnoses.

Neuropathic pain (central)

Pain caused by a lesion or disease of the central somatosensory nervous system.

Neuropathy

A disturbance of function or pathological change in a nerve: in one nerve, mononeuropathy; in several nerves, mononeuropathy multiplex; if diffuse and bilateral, polyneuropathy.

Nociception

The neural process of encoding noxious stimuli.

Nociceptive neuron

A central or peripheral neuron of the somatosensory nervous system that is capable of encoding noxious stimuli.

Nociceptor

A high-threshold sensory receptor of the peripheral somatosensory nervous system that is capable of transducing and encoding noxious stimuli.

Noxious stimulus

Refers to a stimulus that is damaging or threatens damage to normal tissues.

Pain threshold

Defined as the least experience of pain which a subject can recognize. Traditionally the threshold has often been defined as the least stimulus intensity at which a subject perceives pain. Properly defined, the threshold is really the experience of the patient, whereas the intensity measured is an external event.

Pain tolerance level

Defined as the greatest level of pain which a subject is prepared to tolerate. As with pain threshold, the pain tolerance level is the subjective experience of the individual. The stimuli which are normally measured in relation to its production are the pain tolerance level stimuli and not the level itself.

Paresthesia

An abnormal sensation, whether spontaneous or evoked.

2. APPENDIX TO CHAPTER ON NEUROMODULATION TECHNOLOGY

2.1. Overview of conditions and therapies commonly associated with neuromodulation

Source: International Neuromodulation Society (INS) available from http://www.neuromodulation.com

Conditions in which selected patients are claimed to respond to neuromodulation therapies include:

- Brain-Computer Interface in Movement Disorders;
- Complex Regional Pain Syndrome ;
- Gastric Disorders;
- Refractory to medical treatment;
- Medically Refractory Headache;
- Parkinson's Disease;
- Urologic Disorders.

Neuromodulation therapies using electrical stimulation:

- Cerebral (Motor) Cortex Stimulation;
- Cochlear Implants;
- Cortical Stimulation;
- Deep Brain Stimulation;
- Diaphragm (Phrenic) Pacing;
- Occipital Nerve Stimulation Stimulation;
- Peripheral Nerve Stimulation;
- Pudendal Nerve Stimulation;
- Retinal Stimulation;
- Sacral (Urologic) Nerve Stimulation;
- Spinal Cord Stimulation;
- Trigeminal Nerve Stimulation;

- Vagus (Vagal) Nerve Stimulation;
- Neuromodulation therapies using targeted drug delivery;
- Intrathecal/Intraspinal;
- Intraventricular.

3. APPENDIX TO CHAPTER ON EFFECTIVENESS AND SAFETY

3.1. Introduction

All searches for the systematic review of interventional research were run in early 2012. The additional searches for the selected review of observational evidence were run in June and July 2012.

3.2. Search strategies systematic literature review

3.2.1. Pubmed through Medline

Search for systematic reviews and meta-analyses

Run on January 20, 2012 (92 citations)

Limits: published from 2002 onwards, in Dutch, English, French, German or Spanish

The filter used for systematic reviews and meta-analyses was published by Hunt et al. Ann Intern Med 1997;126:532-538.

("Electric Stimulation Therapy"[Mesh] OR "Infusion Pumps, Implantable"[Mesh] OR "Spinal Cord/therapy"[Mesh] OR neuromodulat* OR SCS OR IADP OR (spinal AND cord AND stimulation) OR (intrathecal AND analgesic AND drug AND pump) OR (intrathecal AND (analgesic OR morphine OR morfine OR drug) AND pump))

AND

("Chronic Pain"[Mesh] OR "Pain, Intractable"[Mesh] OR "Neuralgia"[Mesh] OR "Failed Back Surgery Syndrome"[Mesh] OR "Low Back Pain"[Mesh] OR ("Pain/prevention and control"[Mesh] AND chronic) OR ((chronic OR refractory OR intractable OR persist*) AND pain) OR "Peripheral Vascular Diseases"[Mesh] OR "Thromboangiitis Obliterans"[Mesh] OR critical limb ischaemia OR critical limb ischemia OR buergers disease OR buerger disease OR buerger´s disease OR raynaud disease OR raynauds disease OR "Polyneuropathies"[Mesh] OR polyneuropath* OR (angina AND (refractory OR intractable OR persist*)) OR "Coronary Vasospasm"[Mesh] or vasospas*)

AND

("meta-analysis" [pt] OR "meta-anal*" [tw] OR "metaanal*" [tw] OR ("quantitativ* review*" [tw] OR "quantitative* overview*" [tw]) OR ("systematic* review*" [tw] OR "systematic* overview*" [tw]) OR ("methodologic* review*" [tw] OR "methodologic* overview*" [tw]) OR ("review" [pt] AND "medline" [tw])

Search for RCTs

Run on February 6, 2012 (597 citations)

Limits: published from June 2007 onwards, in Dutch, English, French, German or Spanish

The filter used for RCTs was published by the Cochrane collaboration and recommended as a highly sensitive search strategy for identifying randomised trials (http://dcc.cochrane.org/beoordelingsformulieren-en-andere-downloads).

("Electric Stimulation Therapy"[Mesh] OR "Infusion Pumps, Implantable"[Mesh] OR "Spinal Cord/therapy"[Mesh] OR neuromodulat* OR SCS OR IADP OR (spinal AND cord AND stimulation) OR (intrathecal AND analgesic AND drug AND pump) OR (intrathecal AND (analgesic OR morphine OR morfine OR drug) AND pump))

AND

("Chronic Pain"[Mesh] OR "Pain, Intractable"[Mesh] OR "Neuralgia"[Mesh] OR "Failed Back Surgery Syndrome"[Mesh] OR "Low Back Pain"[Mesh] OR ("Pain/prevention and control"[Mesh] AND chronic) OR ((chronic OR refractory OR intractable OR persist*) AND pain) "Peripheral Vascular Diseases"[Mesh] OR "Thromboangiitis Obliterans"[Mesh] OR critical limb ischaemia OR critical limb ischemia OR buergers disease OR buerger disease OR buerger´s disease OR raynaud disease OR raynauds disease OR "Polyneuropathies"[Mesh] OR polyneuropath* OR (angina AND (refractory OR intractable OR persist*)) OR "Coronary Vasospasm"[Mesh] or vasospas*

AND

(randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab]) NOT (animals[mh] NOT (animals[mh] AND humans [mh]))

3.2.2. EMBASE through OVID®

Search for systematic reviews

Run on January 20, 2012 (151 citations)

1 Low Back Pain/dt, th, dm (8148)

2 cancer pain/dt, th, dm or chronic pain/dt, th, dm or intractable pain/dt, th, dm or limb pain/dt, th, dm or neuralgia/dt, th, dm (20031)

3 exp pain/dt, th, dm [Drug Therapy, Therapy, Disease Management] (143861)

4 (chronic or refractory or persist$ or intractable).tw. (1257069)

5 3 and 4 (27188)

6 pain.tw. (441024)

7 4 and 6 (91173)

8 exp failed back surgery syndrome/ (399)

9 1 or 2 or 5 or 7 or 8 (112048)

10 peripheral vascular disease/ (15603)

11 critical limb ischaemia.tw. (507)

12 critical limb ischemia.tw. (1665)

13 Thromboangiitis Obliterans/ (3276)

14 buerger's disease.tw. (941)

15 buergers disease.tw. (941)

16 buerger disease.tw. (125)

17 vasculitide$.tw. (2087)

18 Raynaud disease/ (9622)

19 Raynaud$disease.tw. (0)

20 exp Polyneuropathies/ (24485)

21 polyneuropath$.tw. (12504)

22 exp Angina pectoris/ (69425)

23 refractory angina.tw. (773)

24 exp coronary vasospasm/ (4991)

25 vasospas$.tw. (11713)

26 or/9-25 (247908)
27 electrostimulation therapy/ (10017)
28 infusion pump/ (5273)
29 spinal cord/th [Therapy] (1)
30 neuromodulation/ (17657)
31 neuromodulat$.tw. (9995)
32 SCS.mp. (4039)
33 IADP.mp. (7)
34 exp intrathecal drug administration/ (15698)
35 (spinal and cord and stimulation).tw. (12880)
36 spinal cord stimulation/ (2835)
37 (intrathecal and analgesic and drug and pump).tw. (30)
38 (intrathecal and (analgesic or morphine or morfine or drug) and pump).tw. (399)
39 or/27-38 (69220)
40 26 and 39 (5654)
41 exp Meta Analysis/ (59199)
42 ((meta adj analy$) or metaanalys$).tw. (52223)
43 (systematic adj (review$1 or overview$1)).tw. (39670)
44 or/41-43 (107089)
45 cancerlit.ab. (618)
46 cochrane.ab. (24394)
47 embase.ab. (20979)
48 (psychlit or psyclit).ab. (927)
49 (psychinfo or psycinfo).ab. (5049)
50 (cinahl or cinhal).ab. (7418)
51 science citation index.ab. (1695)
52 bids.ab. (398)
53 or/45-52 (36402)
54 reference lists.ab. (7580)
55 bibliograph$.ab. (12667)
56 hand-search$.ab. (3498)
57 manual search$.ab. (1962)
58 relevant journals.ab. (674)
59 or/54-58 (23833)
60 data extraction.ab. (9348)
61 selection criteria.ab. (18076)
62 60 or 61 (26106)
63 review.pt. (1776656)
64 62 and 63 (16082)
65 letter.pt. (765137)
66 editorial.pt. (396266)
67 animal/ (1680441)
68 human/ (12910848)
69 67 not (67 and 68) (1280344)
70 or/65-66,69 (2428818)
71 44 or 53 or 59 or 64 (135150)
72 71 not 70 (129722)
73 40 and 72 (186)
74 limit 73 to ((dutch or english or french or german or spanish) and yr="2002 -Current") (151)

Search for RCTs

Run on February 6, 2012 (500 citations)

1 Clinical trial/ (829111)
2 Randomized controlled trial/ (300690)
3 Randomization/ (55865)
4 Single blind procedure/ (14884)
5 Double blind procedure/ (105828)
6 Crossover procedure/ (31994)

7 Placebo/ (206071)
8 Randomi?ed controlled trial$.tw. (69294)
9 Rct.tw. (8616)
10 Random allocation.tw. (1137)
11 Randomly allocated.tw. (16559)
12 Allocated randomly.tw. (1759)
13 (allocated adj2 random).tw. (773)
14 Single blind$.tw. (11844)
15 Double blind$.tw. (128268)
16 ((treble or triple) adj blind$).tw. (283)
17 Placebo$.tw. (171265)
18 Prospective study/ (183751)
19 or/1-18 (1198592)
20 Case study/ (14898)
21 Case report.tw. (224292)
22 Abstract report/ or letter/ (829016)
23 or/20-22 (1063932)
24 19 not 23 (1164154)
25 Low Back Pain/dt, th, dm (8148)
26 cancer pain/dt, th, dm or chronic pain/dt, th, dm or intractable pain/dt, th, dm or limb pain/dt, th, dm or neuralgia/dt, th, dm (20031)
27 exp pain/dt, th, dm [Drug Therapy, Therapy, Disease Management] (143861)
28 (chronic or refractory or persist$ or intractable).tw. (1257069)
29 27 and 28 (27188)
30 pain.tw. (441024)
31 28 and 30 (91173)
32 exp failed back surgery syndrome/ (399)
33 25 or 26 or 29 or 31 or 32 (112048)
34 peripheral vascular disease/ (15603)
35 critical limb ischaemia.tw. (507)
36 critical limb ischemia.tw. (1665)
37 Thromboangiitis Obliterans/ (3276)
38 Buerger's disease.tw. (941)
39 buergers disease.tw. (941)
40 buerger disease.tw. (125)
41 vasculitide$.tw. (2087)
42 Raynaud$disease.tw. (0)
43 Raynaud disease/ (9622)
44 exp Polyneuropathies/ (24485)
45 polyneuropath$.tw. (12504)
46 exp Angina pectoris/ (69425)
47 refractory angina.tw. (773)
48 exp coronary vasospasm/ (4991)
49 vasospas$.tw. (11713)
50 or/33-49 (247908)
51 electrostimulation therapy/ (10017)
52 infusion pump/ (5273)
53 spinal cord/th [Therapy] (1)
54 neuromodulation/ (17657)
55 neuromodulat$.tw. (9995)
56 SCS.mp. (4039)
57 IADP.mp. (7)
58 exp intrathecal drug administration/ (15698)
59 (spinal and cord and stimulation).tw. (12880)
60 spinal cord stimulation/ (2835)
61 (intrathecal and analgesic and drug and pump).tw. (30)
62 (intrathecal and (analgesic or morphine or morfine or drug) and pump).tw. (399)
63 or/51-62 (69220)

64 50 and 63 (5654)

65 24 and 64 (1152)

66 limit 65 to ((dutch or english or french or german or spanish) and yr="2007 -Current") (500)

3.2.3. Other searches

Other reviews (DARE), methods studies, health technology assessments (NHS HTA) and economic evaluations (NHS EED) through the Cochrane Library

Run on January 20, 2012

#1 MeSH descriptor **Pain, Intractable** explode all trees 224

#2 MeSH descriptor **Pain** explode all trees 28635

#3 ((chronic OR refractory OR intractable OR persist*) AND pain) 10709

#4 (chronic OR refractory OR intractable OR persist*) 73110

#5 (#2 AND #4) 5079

#6 MeSH descriptor **Failed Back Surgery Syndrome** explode all trees 10

#7 (#1 OR #3 OR #5 OR #6) 11681

#8 MeSH descriptor **Electric Stimulation Therapy** explode all trees 3935

#9 MeSH descriptor **Infusion Pumps, Implantable** explode all trees 127

#10 neuromodulat* OR SCS OR IADP 487

#11 spinal AND cord AND stimulation 594

#12 intrathecal AND analgesic AND drug AND pump 28

#13 intrathecal AND (analgesic OR morphine OR morfine OR drug) AND pump 113

#14 (#8 OR #9 OR #10 OR #11 OR #12 OR #13) 4878

#15 MeSH descriptor Peripheral Vascular Diseases explode all trees 242

#16 MeSH descriptor Thromboangiitis Obliterans explode all trees 6

#17 critical limb ischaemia 169

#18 critical limb ischemia 260

#19 buergers disease 8

#20 buerger disease 38

#21 buerger´s disease 24

#22 raynaud disease 376

#23 raynauds disease 249

#24 MeSH descriptor Polyneuropathies explode all trees 6

#25 polyneuropath* 412

#26 angina AND (refractory OR intractable OR persist*) 688

#27 MeSH descriptor Coronary Vasospasm explode all trees 6

#28 vasospas* 676

#29 (#7 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28) 13495

#30 (#14 AND #29), from 2002 to 2012 216

3.2.4. Cochrane Central Register of Controlled Trials (CENTRAL)

Run on February 6, 2012 (Issue 1 2012) (99 citations)

#1 MeSH descriptor **Pain, Intractable** explode all trees 224

#2 MeSH descriptor **Pain** explode all trees 28635

#3 ((chronic OR refractory OR intractable OR persist*) AND pain) 10709

#4 (chronic OR refractory OR intractable OR persist*) 73110

#5 (#2 AND #4) 5079

#6 MeSH descriptor **Failed Back Surgery Syndrome** explode all trees 10

#7 (#1 OR #3 OR #5 OR #6) 11681

#8 MeSH descriptor **Electric Stimulation Therapy** explode all trees 3935

#9 MeSH descriptor **Infusion Pumps, Implantable** explode all trees 127

#10 neuromodulat* OR SCS OR IADP 487

#11 spinal AND cord AND stimulation 594

#12 intrathecal AND analgesic AND drug AND pump 28

#13 intrathecal AND (analgesic OR morphine OR morfine OR drug) AND pump 113

#14 (#8 OR #9 OR #10 OR #11 OR #12 OR #13) 4878

#15 MeSH descriptor Peripheral Vascular Diseases explode all trees 242

#16 MeSH descriptor Thromboangiitis Obliterans explode all trees 6
#17 critical limb ischaemia 169
#18 critical limb ischemia 260
#19 buergers disease 8
#20 buerger disease 38
#21 buerger´s disease 24
#22 raynaud disease 376
#23 raynauds disease 249
#24 MeSH descriptor Polyneuropathies explode all trees 6
#25 polyneuropath* 412
#26 angina AND (refractory OR intractable OR persist*) 688
#27 MeSH descriptor Coronary Vasospasm explode all trees 6
#28 vasospas* 676
#29 (#7 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28) 13495
#30 (#14 AND #29), from 2007 to 2012 107

3.3. Evidence from interventional studies

3.3.1. Overview of systematic reviews and selected RCTs

Table 23 – General overview of 17systematic reviews on spinal cord stimulation

Study	Target population systematic review	Search up to	Relevant RCTs included	Meta-analysis of included RCTs
Bala 2008[60]	Failed back surgery syndrome	January 2008	2 RCTs in patients with failed back surgery syndrome[39, 84]	No
Börjesson 2008[61]	Severe angina	May 2007	5 RCTs in patients with refractory angina[53, 54, 90-92, 94, 155]	No
Chou 2009[62]	Low back pain	July 2008	2 RCTs in patients with failed back surgery syndrome[39, 84]	No
Frey 2009[63]	Failed back surgery syndrome	December 2008	2 RCTs in patients with failed back surgery syndrome[39, 84, 85, 156]	No
Grabow 2003[64]	Complex regional pain syndrome	April 2002	1 RCT in patients with complex regional pain syndrome type I[86]	No
Klomp 2009[56]	Critical leg ischemia	Not reported	5 RCTs in patients with critical leg ischemia[157-161]	Yes
Mailis-Gagnon 2004[65]	Chronic pain	September 2003	1 RCT in patients with complex regional pain syndrome type I[86] 1 RCT in patients with failed back surgery syndrome[156, 162]	No
Manchikanti 2010[66]	Low back pain	July 2008	2 RCTs in patients with failed back surgery syndrome[39, 84, 85]	No
Medical Advisory Secretariat 2005[67]	Neuropathic pain	January 2005	1 RCT in patients with complex regional pain syndrome type I[88] 1 RCT in patients with failed back surgery syndrome[39]	No
Middleton 2003[34]	Not specified	April 2003	1 RCT in patients with failed back surgery syndrome[156, 162, 163] 1 RCT in patients with complex regional pain syndrome type I[86, 87, 164] 2 RCTs in patients with critical limb ischemia[157, 161, 165-167] 4 RCTs in patients with refractory angina[54, 90, 92, 93, 155, 168] 1 RCT in patients with painful diabetic neuropathy[169]	No
Simpson 2009[12]	Chronic pain of neuropathic or ischemic origin	August 2007	2 RCTs in patients with failed back surgery syndrome[39, 68, 84, 156, 162] 1 RCT in patients with complex regional pain syndrome type I[86, 88, 170] 4 RCTs in patients with critical limb ischemia[157-159, 161, 165-167, 171-174] 4 RCTs in patients with refractory angina[54, 90, 91, 93, 94, 155]	No
Taylor 2005[68]	Failed back surgery syndrome	January 2002	1 RCT in patients with failed back surgery syndrome[156, 162, 163]	No

Study	Target population systematic review	Search up to	Relevant RCTs included	Meta-analysis of included RCTs
Taylor 2006A[69]	Complex regional pain syndrome	January 2002	1 RCT in patients with complex regional pain syndrome type I[86, 164]	No
Taylor 2006B[70]	Complex regional pain syndrome or failed back surgery syndrome	Not reported	1 RCT in patients with complex regional pain syndrome type I[86] 1 RCT in patients with failed back surgery syndrome[39, 156]	No
Taylor 2009[71]	Refractory angina	February 2008	7 RCTs in patients with refractory angina[53, 54, 90-94, 155, 168, 175, 176]	Yes
Turner 2004[72]	Complex regional pain syndrome or failed back surgery syndrome	May 2003	1 RCT in patients with complex regional pain syndrome type I[86, 87]	No
Ubbink 2005-2009[57, 58]	Non-reconstructable chronic critical leg ischemia	September 2008	5 RCTs and 1 CT in patients with critical limb ischemia[112, 157-159, 165-167, 171]	Yes

Abbreviations: CT: controlled trial; RCT: randomised controlled trial

Table 24 – General overview of six systematic reviews on intrathecal analgesic delivery pumps

Study (ref)	Target population systematic review	Search up to	Relevant RCTs included	Meta-analysis of included RCTs
Hayek 2011[74]	Chronic cancer and non-cancer pain	December 2010	1 RCT in patients with cancer and refractory pain[95]	No
Manchikanti 2010[66]	Low back pain	July 2008	0 RCTs	Not applicable
Patel 2009[75]	Chronic non-cancer pain	December 2008	0 RCTs	Not applicable
Simpson 2003[76]	Chronic pain and spasticity	April 2003	1 RCT in patients with cancer and refractory pain[95]	No
Teasell 2010[78]	Spinal cord injury	June 2009	1 RCT in patients with neuropathic pain[177]	No
Turner 2007[79]	Chronic non-cancer pain	October 2005	0 RCTs	Not applicable

Abbreviations: RCT: randomised controlled trial

Table 25 – General overview of RCTs included in systematic reviews on spinal cord stimulation, per population category, and assessment of those RCTs for inclusion

Study population	Number of trials	RCTs included	Included in systematic review	Control treatment	In- or excluded in present review	Reason for exclusion	Additional publications identified in search for RCTs
Angina	8	De Jongste 1993[53]	Börjesson 2008[61]	No SCS (angina medication was continued in both treatment groups)	Included	Not applicable	None
		De Jongste 1994[155]	Börjesson 2008[61] Middleton 2003[34] Simpson 2009[12] Taylor 2009[71]	Before-after study	Excluded	´Before-after´ design	None
		Di Pede 2001[168]	Middleton 2003[34] Taylor 2009[71]	Spinal cord stimulation switched on and off in the same patient	Excluded	All patients had been on SCS for a mean of 39 months before the trial	None
		Eddicks 2007[176]	Taylor 2009[71]	Spinal cord stimulation off	Excluded	All patients were on SCS therapy for at least three months	None
		ESBY 1998[90-93]	Börjesson 2008[61] Middleton 2003[34] Simpson 2009[12] Taylor 2009[71]	Coronary artery bypass graft	Included	Not applicable	None
		Hautvast 1998[54]	Börjesson 2008[61] Middleton 2003[34] Simpson 2009[12] Taylor 2009[71]	Sham SCS + standard treatment	Included	Not applicable	None
		Jessurun 1999[175]	Taylor 2009[71]	Spinal cord	Excluded	All patients had been on	None

Study population	Number of trials	RCTs included	Included in systematic review	Control treatment	In- or excluded in present review	Reason for exclusion	Additional publications identified in search for RCTs
				stimulation off		SCS therapy before the trial	
		McNab 2006[94]	Börjesson 2008[61] Simpson 2009[12] Taylor 2009[71]	Percutaneous myocardial laser revascularizatio n	Included	Not applicable	Dyer 2008[110] Khan 2008[178]
Complex regional pain syndrome	1	Kemler 2000[86-88, 164]	Grabow 2003[64] Mailis-Gagnon 2003[65] Medical Advisory Secretariat 2005[67] Middleton 2003[34] Simpson 2009[12] Taylor 2006A[69] Taylor 2006B[70] Turner 2004[72]	Physical therapy	Included	Not applicable	Kemler 2008[121]
Diabetic neuropathy	1	Tesfaye 1996[169]	Middleton 2003[34]	No RCT	Excluded	No control treatment beyond the SCS test period	None
Failed back surgery syndrome	2	North 2005[39, 156, 162, 163]	Bala 2008[60] Chou 2009[62] Frey 2009[63] Mailis-Gagnon 2003[65] Manchikanti 2010[66] Medical Advisory Secretariat 2005[67] Middleton 2003[34] Taylor 2005[68] Taylor 2006B[70]	Repeated lumbosacral spine surgery	Included	Not applicable	None

Study population	Number of trials	RCTs included	Included in systematic review	Control treatment	In- or excluded in present review	Reason for exclusion	Additional publications identified in search for RCTs
		Kumar 2007[68, 84, 85]	Bala 2008[60] Chou 2009[62] Frey 2009[63] Manchikanti 2010[66] Simpson 2009[12]	CMM	Included	Not applicable	Eldabe 2010[179] Eldabe 2009A[180] Eldabe 2009B[181] Kumar 2009[182] Kumar 2010A[183] Kumar 2010B[184] Manca 2008[40]
Limb ischemia	5 + 1 CT	Amann 2003[89] (CT)	Ubbink 2005-2009[57, 58]	Best medical therapy	Included	Though we had not predefined the selection of controlled trials we decided to include the systematic review of Ubbink 2005-2009[57, 58] that included Amann 2003[89]	None
		Claeys 1996[159, 172-174]	Klomp 2009[56] Simpson 2009[12] Ubbink 2005-2009[57, 58]	Conservative medical therapy	Included	Not applicable	None
		ESES 1999[112, 161, 165-167]	Klomp 1999[161] Middleton 2003[34] Simpson 2009[12] Ubbink 2005-2009[57, 58]	Best medical therapy	Included	Not applicable	None
		Jivegard 1995[157]	Klomp 2009[56] Middleton 2003[34] Simpson 2009[12] Ubbink 2005-2009[57, 58]	Oral analgesic treatment	Included	Not applicable	None
		Spincemaille 2000[160]	Klomp 2009[56] Ubbink 2005-2009[57, 58]	Best medical therapy	Included	Not applicable	None

Study population	Number of trials	RCTs included	Included in systematic review	Control treatment	In- or excluded in present review	Reason for exclusion	Additional publications identified in search for RCTs
		Suy 1994[158] #	Klomp 2009[56] Simpson 2009[12] Ubbink 2005-2009[57, 58]	Conservative therapy	Included	Not applicable	None

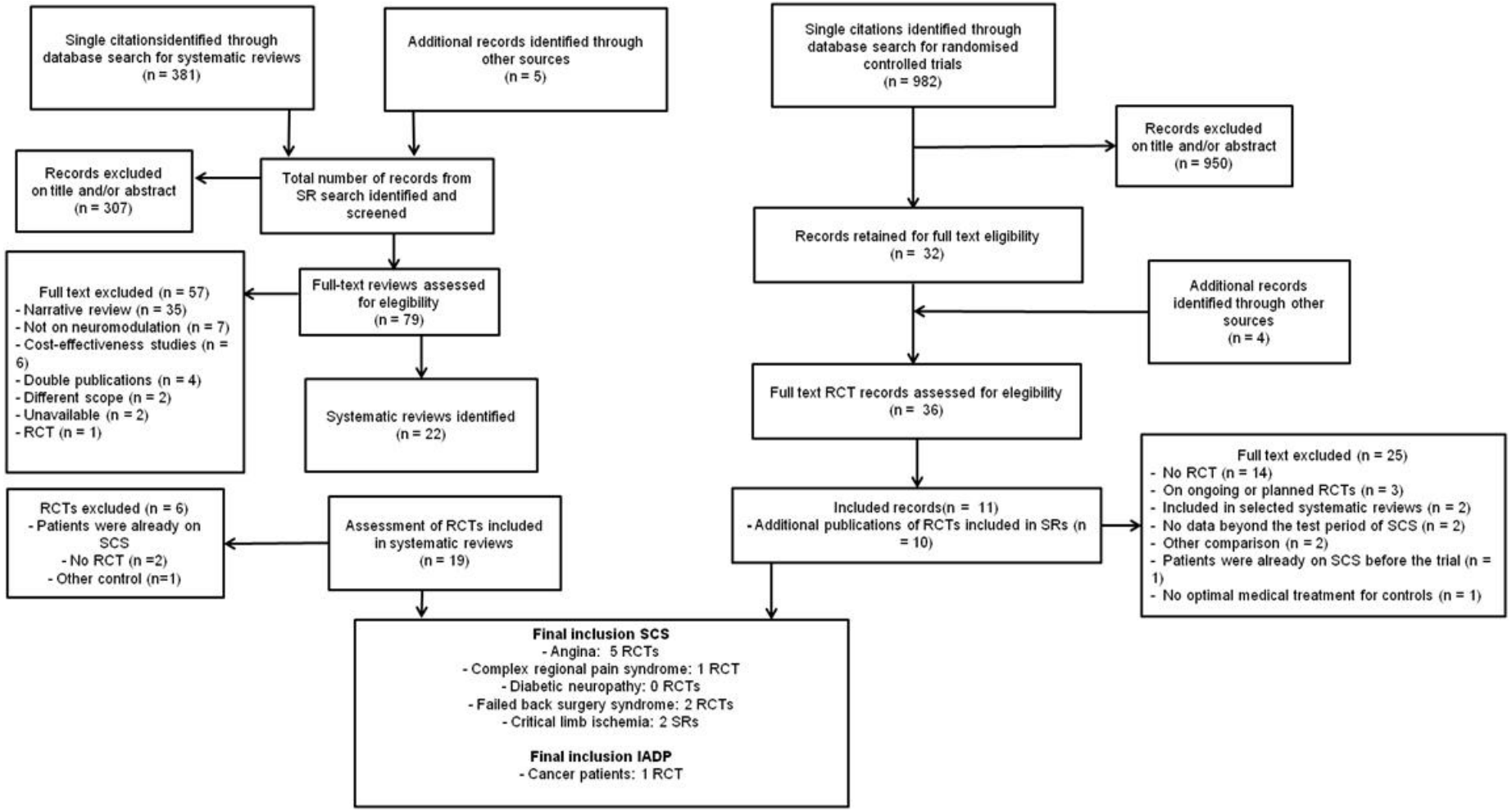
Abbreviations: CT: controlled trial; RCT: randomised controlled trial
#: publication unavailable. Eligibility assessed based on the information available in Klomp 2009 and Ubbink 2005-2009

Table 26 – General overview of RCTs included in systematic reviews on intrathecal analgesic delivery pumps, per population category, and assessment of those randomised trials for inclusion

Study population	Number of trials	RCTs included	Included in systematic review	Control treatment	In- or excluded in present review	Reason for exclusion	Additional publications identified in search for RCTs
Cancer patients	1	Smith 2002[95]	Hayek 2011[74]	Comprehensive medical management	Included	Not applicable	None
Spinal cord injury	1	Siddal 2000[177]	Teasell 2010[78]	Placebo	Excluded	Patients were their own control. No other pain medication except paracetamol allowed during either treatment	None

Abbreviations: RCT: randomised controlled trial

Figure 15 – General overview of the search and selection process



Abbreviations: IADP: intrathecal analgesic delivery pump; RCT: randomised controlled trial; SCS: spinal cord stimulation; SR: systematic review

3.3.2. Assessment of methodological quality

Table 27 – Risk of bias in RCTs on spinal cord stimulation and intrathecal analgesic delivery pumps

	De Jongste 1993 (SCS)	ESBY 1998 (SCS)	Hautvast 1998 (SCS)	Lanza 2011 (SCS)	Mc Nab 2006 (SCS)	Kemler 2000 (SCS)	North 2005 (SCS)	Kumar 2007 (SCS)	Smith 2002 (IADP)
Random sequence generation (selection bias)	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	Unclear risk
Allocation concealment (selection bias)	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk
Blinding of participants and personnel (performance bias)	High risk	High risk	Low risk	High risk	High risk	High risk	High risk	High risk	High risk
Blinding of outcome assessment (detection bias)	High risk	High risk	Low risk	Unclear risk	High risk	High risk	High risk	High risk	High risk
Incomplete outcome data (attrition bias)	Low risk	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk	High risk
Selective reporting (reporting bias)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Other bias (industry sponsored)	Unclear risk	Low risk	Low risk	High risk	High risk	Low risk	High risk	High risk	High risk

Table 28 – AMSTAR checklist of systematic reviews on spinal cord stimulation in patients with critical limb ischemia

	Klomp 2009[56]	Ubbink 2005-2009[57, 58]
Was an 'a priori' design provided?	Yes	Yes
Was there duplicate study selection and data extraction?	Can´t answer	Yes
Was a comprehensive literature search performed?	No	Yes
Was the status of publication (i.e. grey literature) not an exclusion criterion?	Can´t answer	Yes
Was a list of studies (included and excluded) provided?	No	Yes
Were the characteristics of the included studies provided?	No	Yes#
Was the scientific quality of the included studies assessed and documented?	Yes	Yes

	Klomp 2009[56]	Ubbink 2005-2009[57, 58]
Was the scientific quality of the included studies used appropriately in formulating conclusions?	No	Yes
Were the methods used to combine the findings of studies appropriate?	Yes	Yes
Was the likelihood of publication bias assessed?	No	No
Was the conflict of interest stated?	No	Yes

 # Funding of studies was a predetermined item to be collected, however, this was not reported on

3.3.3. Evidence and GRADE tables

Table 29 – Evidence table of RCTs on spinal cord stimulation in patients with refractory angina

Study	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results other relevant outcome(s)	Critical appraisal of study quality
De Jongste 1993[53]	• Design: RCT • Funding: no reported • Setting: single centre, the Netherlands • Sample size: n=24 • Duration: 2 months	• Eligibility: medically refractory angina (on pharmacological optimal drug treatment for at least 1 m); no possibilities for revascularisation; proven CAD and ischemia; between 18-76 y of age • Exclusion: short life expectancy; inability to perform exercise testing • Patients characteristics:	SCS vs no SCS	ADL scoring at 2 m (SD): 2.0 (0.6) vs 1.3 (0.3) (p<0.01) Short-acting glyceryl trinitrate intake/week at 2 m (SD): 1.7 (1.7) vs 12.0 (4.0) (p<0.01) Anginal attacks/week (SD): 6.3 (5.1) vs 16.3 (7.9) (p=0.01) Rate pressure product x 100 (SD): 142 (44) vs 137 (34) (p=0.77) Total exercise time (minutes) (SD): 10.8 (4.1) vs 10.8 (4.0) (p=1.0) Time to angina (minutes) (SD): 10.9 (3.9) vs 10.4 (4.0)	-	• Randomisation procedure and allocation concealment not reported on • Small sample size • Non-blinded study • Short follow-up (2 months) • p-values for between-group differences were not reported in the study; those reported here were calculated by us • After 2 months controls got a SCS implanted as well.

Study	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results other relevant outcome(s)	Critical appraisal of study quality
		58% male; mean age: 68.9 y		(p=0.77) Maximum total ST-segment depression (mV) (SD): 0.95 vs 2.02		The reported results for this group were not reported here
ESBY 1998[90-92]	• Design: RCT • Funding: University of Gothenburg, the Swedish National Heart-Lung Foundation, Swedish Medical Research Council • Setting: two centres, Sweden • Sample size: n=104 • Duration: January 1992-March 1995	• Eligibility: only symptomatic indication for CABG (i.e. no prognostic benefit), to run an increased risk of surgical complications and unsuitable for PCI • Exclusion: unsuitable for CABG; unable to manage the SCS device; myocardial infarction within the last 6 m • Patients characteristics: 80% male; mean age: 60.3 y	SCS vs CABG	Nitrate consumption at 6 m (doses/week) (SD): 4.1 (10.5) vs 3.1 (8.7) (ns) Anginal attacks/week at 6 m (SD): 4.4 (7.4) vs 5.2 (10.3) (ns) Self-estimated treatment effect at 6 m (% better or symptom free): 83.7% vs 79.5% (ns) Maximum workload capacity at 6 m (W) (SD): 92.2 (33.7) vs 99.0 (28.0) (p=0.02) ST-segment depression on maximum workload at 6 m (mm) (SD): -1.95 (1.18) vs -0.68 (1.52) (p<0.01) ST-segment depression on comparable workload at 6 m (mm) (SD): -1.66 (1.24) vs -0.46	Mortality at 6 m: 1 vs 7 (p=0.02). 3 out of 7 deaths in the CABG group occurred before surgery Mortality at 2 y: 5 vs 10 (ns) Mortality at 3 y: 8 vs 12 (ns) Mortality at 5 y: 13 vs 16 (ns) Non-fatal morbidity at 6 m: 7 vs 7 (ns) Cerebrovascular morbidity at 6 m: 2 vs 8 (p=0.03) Total morbidity at 6 m: 8 vs 14 (p=0.08) There were no significant differences in quality of life between groups at 6 m or 4.8 y Three patients had their spinal cord electrodes surgically corrected. The stimulator had to be removed because of	• Randomisation procedure and allocation concealment not reported on • Non-blinded study • There were more current smokers in the CABG group and more patients with nephrologic disease in the SCS group • ITT analyses • Exercise testing was performed with SCS off. The authors conclude that exercise testing should be performed with SCS on

Study	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results other relevant outcome(s)	Critical appraisal of study quality
				(1.13) (p<0.01) Rate-pressure product on maximum workload at 6 m (mm Hg/minx103) (SD): 21.2 (6.9) vs 25.4 (5.6) (p<0.01) Rate-pressure product on comparable workload at 6 m (mm Hg/minx103) (SD): 20.6 (6.5) vs 23.0 (5.4) (p=0.03)	infection in one patient. No additional infections occurred in the SCS group. The average life span of the pulse generators before replacement was 3.6 y	
Hautvast 1998[54]	• Design: RCT • Funding: the Netherlands Heart Foundation • Setting: single centre, the Netherlands • Sample size: n=25 • Duration: not reported	• Eligibility: chronic intractable angina class III or IV NYHA despite maximal tolerable dosage of beta-blocking agents, calcium antagonists and long-acting nitrates; established ischemia during treadmill testing; CAD in a recent coronary angiogram; no PCI or CABG	SCS (three times daily for 1 hour and during angina) vs inactive stimulation (sham SCS)	Treadmill exercise assessments at 6 weeks: • Time to angina: 319 (SD 85) vs 246 s (SD 97) (p=0.06) • Total exercise duration: 533 (SD 184) vs 427 s (SD 177) (p=0.16) • ST-segment depression at maximal exercise: 0.13 (SD 0.07) vs 0.15 mV (SD 0.11) (p=0.59) • Rate pressure product at maximal exercise: 178 (SD	• No complications in either group • Median (range) ischemic episodes: 0 (0-12) vs 1 (0-14) • Median duration (range) of ischemic episodes (minutes): 0 (0-55.9) vs 1.9 (0-127.1)	• Randomisation procedure and allocation concealment not reported on • Small sample size • Double blinded study • Short follow-up (6 weeks) • Group comparability: more MI in control group; more PCI in experimental group • No drop outs • Statistical analysis was based on

Study	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results other relevant outcome(s)	Critical appraisal of study quality
		options • Exclusion: inability to perform exercise testing; conduction disturbances disabling recognition of ischemia; anatomic inability SCS implantation; age >75 y; ejection fraction <30% • Patients characteristics: 56% male; mean age: 62.5 y		60) vs 131 mmHg x 100/min (SD 51) (p=0.05) • ST-segment depression at comparable workload: 0.11 (SD 0.06) vs 0.13 mV (SD 0.08) (p=0.48) • Rate pressure product at comparable workload: 150 (SD 57) vs 126 mmHg x 100/min (SD 49) (p=0.27) Patients diary assessments at 6 weeks: • Angina attacks per day: 2.3 (SD 1.9) vs 3.2 (SD 1.5) (p=0.26) • Nitrogen consumption (tablets): 1.6 (SD 2.2) vs 2.6 (SD 1.7) (p=0.22) • VAS score (mm): 26 (SD 14) vs 32 (SD 14) (p=0.29) • LASA score (mm):		within-group differences (before-after design) or on a comparison of within-group differences, and not on between group differences at follow-up. The reported outcomes were tested by us, if possible, to detect between-group differences at 6 weeks. Thus, reported p-values were calculated by us

Study	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results other relevant outcome(s)	Critical appraisal of study quality
				68 (SD 10) vs 62 (SD 11) (p=0.17)		
Lanza 2011[83]	• Design: RCT • Funding: Medtronic Italia S.p.A. sponsored the investigator meetings • Setting: multiple centres, Italy • Sample size: n=25 • Duration: October 2005- March 2009	• Eligibility: angina pectoris refractory to optimal medical therapy; stable angina for the past 2 m; documented obstructive CAD or documented previous MI; demonstrated reversible ischemia; unsuited or refused for revascularisation • Exclusion: unstable angina; severe spinal cord disease which could prevent the correct lead positioning for SCS; could not stop an ongoing anticoagulant therapy; needed diathermic treatment;	Paresthesic SCS vs subliminal SCS vs sham SCS	Paresthesic SCS vs sham SCS at 1m: • Mean (range) angina episodes: 2 (0-94) vs 20 (2-27) (p<0.01) • Mean (range) nitroglycerin tablets: 0 (0-29) vs 7 (0-44) (p=0.02) • Mean CCS class (SD): 2.10 (1.1) vs 3.25 (0.9) (p=0.01) • Mean VAS (mm) (SD): 67.0 (17) vs 45.0 (14) (p<0.01) • SAQ physical limitation (SD) : 66.3 (20) vs 38.6 (18) • SAQ angina stability (SD): 76.0 (8) vs 47.5 (26) (p<0.01) • SAQ angina frequency (SD): 79.0 (24) vs 43.7 (30) (p<0.01) • SAQ treatment satisfaction (SD): 62.7 (9) vs 47.7 (15)	Paresthesic SCS vs subliminal SCS at 3m: • Mean (range) angina episodes: 1 (0-30) vs 9 (1-30) (p<0.01) • Mean (range) nitroglycerin tablets: 0.5 (2-30) vs 1.5 (0-15) (p=0.24) • Mean CCS class (SD): 2.33 (0.6) vs 2.17 (0.7) (p=0.46) • Mean VAS (mm) (SD): 58.7 (15) vs 58.3 (15) (p=0.33) • SAQ physical limitation (SD) : 57.8 (16) vs58.5 (18) (p=0.88) • SAQ angina stability (SD): 61.7 (23) vs 63.3 (14) (p=0.9) • SAQ angina frequency (SD): 62.5 (32) vs 60.8 (19) (p=0.34) • SAQ treatment satisfaction (SD): 57.2 (14) vs 57.2 (10)	• Randomisation procedure and allocation concealment not reported on • Small sample size • Single-blinded study • Short follow-up (1 month for comparisons to sham SCS and 3 m for paresthesic vs subliminal SCS) • Patients were excluded from the study if they did not show a correct paresthesic coverage of angina pain in the tests performed during the SCS device implant • In 10 out of 25 patients a stress test could not be performed (risk of attrition bias)

Study	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results other relevant outcome(s)	Critical appraisal of study quality
		female patients in fertile age; life expectancy < 6 m; enrolled in other studies • Patients characteristics: 76% male		• SAQ disease perception: 52.7 (21) vs 30.9 (14) The only statistical significant difference at 1 m between paresthesic SCS and subliminal SCS was the use of nitroglycerin tablets. There were no statistical differences between subliminal SCS and sham SCS at 1m	(p=0.39) • SAQ disease perception: 42.2 (20) vs 48.2 (14) (p=0.37)	
McNab 2006[94] Dyer 2008[110] Khan 2008[178]	• Design: RCT • Funding: Medtronic SA • Setting: Single centre, United Kingdom • Sample size: n=68 • Duration: December 2000-December 2003	• Eligibility: patients with Canadian Cardiovascular Society class 3/4 angina despite maximally tolerated anti-anginal medication, and reversible perfusion defects; angiographically documented CAD unsuitable	SCS (three times daily for 1 hour and during angina) vs PMR	Difference in mean total treadmill exercise time at 12 m (CI): 0.59 (-1.02 to 2.20) (p=0.47) Difference in mean time to angina at 12 m (CI): 1.23 (-0.61 to 3.07) (p=0.19) No angina during exercise at 12 m: 37% vs 33% (p=1.00) Difference in mean treadmill exercise time at 24 m (CI): 0.05 (-2.08 to 2.18) (p=0.96)	Change in CCS class ≥2 at 12 m: 37% vs 20% (p=0.17) Change in CCS class ≥2 at 24 m: 32% vs 19% (p=0.49) No significant differences in health-related quality of life at 12 or 24 m No significant differences in medication use at 24 m Safety at 12 m:	• Single blinded study • Similar rate of withdrawals and loss to follow-up • ITT analysis • Adverse events at 12 months differed between publications

Study	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results other relevant outcome(s)	Critical appraisal of study quality
		for conventional revascularizatio n • Exclusion: myocardial wall thickness <8 mm in the areas to be treated by PMR; implanted pacemakers or defibrillators or co-morbidity of greater significance than angina pectoris • Patients characteristics: 88% male; mean age: 63.5 y		Difference in mean time to angina at 24 m (CI): 0.91 (-2.67 to 4.49) (p=0.62) No angina during exercise at 24 m: 50% vs 33% (p=not reported)	• Adverse events: 57 vs 26 (p<0.01) • Excluding SCS/PMR related events: 30 vs 23 (p=0.342) • Severe adverse events: 41 vs 24 (p=0.039) (events requiring admission, prolonged stay in hospital, surgery, or were life threatening or ultimately resulted in death) Safety at 24 m: • Adverse events: 69 vs 59 (ns) • Excluding SCS/PMR related events: 47 vs 52 (ns) • Severe adverse events: 62 vs 54 (ns) Survival at 24 m: 85% vs 94% (p=0.46) There was no significant difference in myocardial perfusion at 12 m	

Abbreviations: ADL: activities of daily living; CABG: coronary artery bypass grafting; CAD: coronary artery disease; mm: millimetre; CI: confidence interval; CCS: Canadian Cardiovascular Society; ITT: intention to treat analysis; m: months; MI: myocardial infarction; LASA: linear analogue self assessment scale; m: months; mm: millimetre; ns: non-significant; NYHA: New York Heart Association; p: p-value; PCI: percutaneous coronary intervention; PMR: percutaneous myocardial laser revascularization; RCT: randomised controlled trial; s: seconds; SAQ: Seattle Angina Questionnaire; SCS: spinal cord stimulation; SD: standard deviation; y: years; VAS: visual analogue score

Table 30 – GRADE assessment of the outcomes of five RCTs on spinal cord stimulation in patients with refractory angina

- Outcome (SD, CI or range) - p-value) - GRADE - Time point	Mortality	Mean nitrate intake/week	Mean anginal attacks/week	Mean total exercise time (minutes or seconds))	Mean time to angina (minutes or seconds)	No angina during exercise	VAS (mm)	LASA
SCS vs no SCS								
De Jongste 1993[53]	-	1.7 (1.7) vs 12.0 (4.0) p<0.01 LOW - 1 study design# - 1 imprecision$ 2 months	6.3 (5.1) vs 16.3 (7.9) p=0.01 LOW - 1 study design# - 1 imprecision$ 2 months	10.8 (4.1) vs 10.8 m (4.0) p=1.0 LOW - 1 study design# - 1 imprecision$ 2 months	10.9 (3.9) vs 10.4 m (4.0) p=0.77 LOW - 1 study design# - 1 imprecision$ 2 months	-	-	-
SCS vs sham SCS								
Hautvast 1998[54]	-	1.6 (2.2) vs 2.6 (1.7) 0.22 VERY LOW † - 1 study design - 1 inconsistency - 1 imprecision 6 weeks	2.3 (1.9) vs 3.2 (1.5) 0.26 VERY LOW † - 1 study design - 1 inconsistency - 1 imprecision 6 weeks	533 (184) vs 427 s (177) p=0.16 MODERATE - 1 imprecision$ 6 weeks	319 (85) vs 246 s (97) p=0.06 MODERATE - 1 imprecision$ 6 weeks	-	26 (14) vs 32 (14) 0.29 VERY LOW † - 1 study design - 1 inconsistency - 1 imprecision 6 weeks	68 (10) vs 62 (11) 0.17 MODERATE - 1 imprecision$ 6 weeks
Lanza 2011[83]	-	0 (0-29) vs 7 (0-44) p=0.02 VERY LOW † 1 month	2 (0-94) vs 20 (2-27) p<0.01 VERY LOW † 1 month	--	-	-	67.0 (17) vs 45.0 (14) p<0.01 VERY LOW † 1 month	-

- Outcome (SD, CI or range) - p-value) - GRADE - Time point	Mortality	Mean nitrate intake/week	Mean anginal attacks/week	Mean total exercise time (minutes or seconds))	Mean time to angina (minutes or seconds)	No angina during exercise	VAS (mm)	LASA
SCS vs CABG								
ESBY 1998[90-92]	1 vs 7 p=0.02 LOW -1 study design# -1 imprecision§ 6 months	4.1 (10.5) vs 3.1 (8.7) ns LOW -1 study design# -1 imprecision§ 6 months	4.4 (7.4) vs 5.2 (10.3) ns LOW -1 study design# -1 imprecision§ 6 months	-	-	-	-	-
	5 vs 10 ns LOW -1 study design# -1 imprecision§ 2 years	-	-	-	-	-	-	-
SCS vs percutaneous myocardial laser revascularisation								
McNab 2006[94, 110, 178]	-	-	-	MD 0.59 (-1.02 to 2.20) p=0.47 LOW -1 study design#	MD 1.23 (-0.61 to 3.07) p=0.91 LOW -1 study design#	37% vs 33% p=1.00 LOW -1 study design# -1	-	-

- Outcome (SD, CI or range) - p-value) - GRADE - Time point	Mortality	Mean nitrate intake/week	Mean anginal attacks/week	Mean total exercise time (minutes or seconds))	Mean time to angina (minutes or seconds)	No angina during exercise	VAS (mm)	LASA
				-1 imprecision£ 12 months	-1 imprecision£ £ 12 months	imprecision£ 12 months		
				MD 0.05 (-2.08 to 2.18) p=0.96 LOW -1 study design# -1 imprecision£ 24 months	0.91 (-2.67 to 4.49) p=0.62 LOW -1 study design# -1 imprecision£ 24 months	50% vs 33% Not reported LOW -1 study design# -1 imprecision£ 24 months		

Table 30 (continued) – GRADE assessment of the outcomes of five RCTs on spinal cord stimulation in patients with refractory angina

- Outcome (SD, CI) - p-value - GRADE - Time point	Mean CCS class	Self estimated treatment effect (%better or symptom free)	ADL score	SAQ physical limitation	SAQ angina stability	SAQ angina frequency	SAQ treatment satisfaction	SAQ disease perception
SCS vs no SCS								
De Jongste 1993[53]	-	-	2.0 (0.6) vs 1.3 (0.3) p<0.01 LOW - 1 study design# - 1 imprecision$ 2 months	-	-	-	-	-
SCS vs sham SCS								
Hautvast 1998[54]	-	-	-	-	-	-	-	-
Lanza 2011[83]	2.10 (1.1) vs 3.25 (0.9) p=0.01 LOW -1 study design# -1 imprecision$ 1 month	-	-	66.3 (20) vs 38.6 (18) Not reported LOW -1 study design# -1 imprecision$ 1 month	76.0 (8) vs 47.5 (26) p<0.01 LOW -1 study design# -1 imprecision$ 1 month	79.0 (24) vs 43.7 (30) p<0.01 LOW -1 study design# -1 imprecision$ 1 month	62.7 (9) vs 47.7 (15) Not reported LOW -1 study design# -1 imprecision$ 1 month	52.7 (21) vs 30.9 (14) Not reported LOW -1 study design# -1 imprecision$ 1 month
SCS vs CABG								
ESBY 1998[90-92]	-	83.7% vs 79.5% ns	-	-	-	-	-	-

		LOW -1 study design# -1 imprecision§ 6 months						
SCS vs percutaneous myocardial laser revascularisation	-							
McNab 2006[94] Dyer 2008[110] Khan 2008[178]	-	-	-	-	-	-	-	-

#: Participants, personnel or outcome assessors were not blinded; in addition in some studies outcome data were incomplete and/or the study was funded by the industry
$: ≤25 participants
†: across the two trials assessing this outcome. Unclear randomisation and concealment procedures and no blinding or unclear whether blinding took place; inconsistent results across studies; ≤25 participants
§: 104 participants; few events
£68 participants
Abbreviations: ADL: activities of daily living; CABG: coronary artery bypass graft; CCS: Canadian Cardiovascular Society; CI: confidence interval; LASA: linear analogue self assessment scale; m: minutes; ns: non-significant; RD: risk difference; RR: risk ratio; s: seconds; SAQ: Seattle Angina Questionnaire; SCS: spinal cord stimulation; SD: standard deviation; VAS: visual analogue scale

Table 31 – Evidence table of one RCT on spinal cord stimulation in patients with complex regional pain syndrome

Study	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results other relevant outcome(s)	Critical appraisal of study quality
Kemler 2000[86-88]	• Design: RCT • Funding: Dutch Health Insurance Council • Setting: single centre, the Netherlands • Sample size: n=54 • Duration: March 1997-July 1998	• Eligibility: 18-65 y; met the diagnostic criteria for reflex sympathetic dystrophy established by the International Association for the Study of Pain with impaired function and symptoms beyond the area of trauma; disease clinically restricted to one hand or foot and affecting the entire hand or foot; lasting for at least 6 m; no sustained response to standard therapy (6 m of physical therapy, sympathetic blockade, transcutaneous electrical nerve stimulation, and pain medication);	SCS + physical therapy vs physical therapy (6 months)	Mean difference VAS at 6 m, 12m and 24 m: p<0.01 Mean VAS at 12 m (SD): 44 mm (28) vs 71 (22) (p<0.01) Score of 6 (much improved) for the global perceived effect at 6 m: 39% vs 6% (p=0.01); at 24 months: 43% vs 6% (p<0.01) EuroQol-5 dimensions at 12 m (SD): 0.43 (0.32) vs 0.22 (0.29) (p=0.02)	Adverse events at 2 y: 38% of patients with a SCS needed reoperation, mainly for electrode migration and pain. 2 patients underwent permanent removal due to recurrent rejection and relapsing ulcerative colitis ascribed to the SCS system, respectively. In all patients some side effects were reported (number of patients): • Change of amplitude by bodily movements (19) • Paresthesiae in other body parts (13) • Pain/irritation from extension lead or plug (11) • Pain/irritation from pulse generator (10) • More pain in other body parts (7) • Disturbed urination (4) • Movements or	• Small sample size • Non-blinded study • Patients without a positive response to SCS (12 out of 36 assigned to SCS) did not receive an SCS implant but were analysed in the SCS group (ITT analysis) • No loss to follow up • Changes in functionality and health related quality of life at 6 and 24 m were reported as differences in within-group changes and are not reported here (all were non-significant)

Study	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results other relevant outcome(s)	Critical appraisal of study quality
		mean VAS ≥ 50 mm • Exclusion: Reynaud's disease; current or previous unrelated neurologic abnormalities; another condition affecting the function of the diseased or contra lateral extremity; a blood-clotting disorder or use of an anticoagulant drug; cardiac pacemaker; serious psychiatric disorders • Patient characteristics: 32% male			cramps resulting from elevated amplitude (3)	

Abbreviations: ITT: intention to treat analysis; m: months; RCT: randomised controlled trial; SCS: spinal cord stimulation; SD: standard deviation; y: years; VAS: visual analogue score

Table 32 – GRADE assessment of the outcomes of one RCTs on spinal cord stimulation in patients with complex regional pain syndrome

- Outcome (SD) - p-value - GRADE - Time point	VAS	Global perceived effect ´much improved´	Euro QoL 5 dimensions
Kemler 2000[86-88]	-	39% vs 6% p=0.01 LOW -1 study design# -1 imprecision$ 6 months	-
	44 mm (28) vs 71 (22) p<0.01 LOW -1 study design# -1 imprecision$ 12months	-	0.43 (0.32) vs 0.22 (0.29) p=0.02 LOW -1 study design# -1 imprecision$ 12 months
	-	43% vs 6% p<0.01 LOW -1 study design# -1 imprecision$ 24 months	-

#: Participants, personnel nor outcome assessors were blinded
$: 54 participants
Abbreviations: SD: standard deviation; VAS: visual analogue scale

Table 33 – Evidence table of two RCTs on spinal cord stimulation in patients with failed back surgery syndrome

Study	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results other relevant outcome(s)	Critical appraisal of study quality
North 2005[39]	• Design: RCT • Funding: Medtronic Inc. • Setting: single centre, United States • Sample size: n=50 • Duration: not reported	• Eligibility: patients with surgically remediable nerve root compression and concordant complaints of persistent or recurrent radicular pain, refractory to conservative care, with or without low back pain, after one or more lumbosacral spine surgeries, and/or mechanical signs and imaging findings of neural compression • Exclusion: disabling neurological deficit in the distribution of a nerve root or roots caused by surgically	SCS vs repeated lumbosacral spine surgery	Crossover at a mean follow-up of 3 y: 5 vs 14 (p=0.02) ≥50% pain relief and treatment satisfaction at a mean follow-up of 3 y: 47% vs 12% (p<0.01)	Improvements in ADL and neurological status were not significant (figures not reported) at a mean follow-up of 3 y Opioid use stable or decreased at a mean follow-up of 3 y: 87% vs 57% (p=0.025) Adverse events: all in SCS group: 1 infection; 3 hardware revisions	• Non-blinded study • Low and non-differential loss to follow up • 39 patients refused randomisation and chose reoperation • Immediate cross-over to the other treatment group was allowed and was the predefined primary outcome • ITT analysis

Study	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results other relevant outcome(s)	Critical appraisal of study quality
		remediable compression; radiographically demonstrated critical cauda equina compression; radiographic evidence of gross instability necessitating fusion: significant untreated dependency on prescription narcotic analgesics or benzodiazepines; major untreated psychiatric co-morbidity; unresolved issues of secondary gain; a concurrent clinically significant or disabling chronic pain problem; a chief complaint of axial pain				

Study	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results other relevant outcome(s)	Critical appraisal of study quality
		exceeding radiculair pain • Patient characteristics: 48% male; mean age (SD): 52.0 y (13.5); mean prior operations (SD): 2.5 (1.1)				
Kumar 2007[84, 85]	• Design: RCT • Funding: Medtronic Inc. • Setting: multicenter, worldwide • Sample size: n=100 • Duration: April 2003-June 2005	• Eligibility: ≥18 y; neuropathic pain of radicular origin predominantly in the legs, of an intensity ≥ 50 mm VAS, for ≥6 m after ≥1 anatomically successful surgery for herniated disc • Exclusion: another clinically significant or disabling chronic pain condition; expected inability to receive or	SCS vs CMM (including oral medications, nerve blocks, epidural corticosteroids, physical and psychological rehabilitative therapy, and/or chiropractic care; excluding other invasive therapy, such as spinal surgery or implantation of an intrathecal drug delivery system)	≥50% leg pain relief at 6 m: 48% vs 9% (p<0.01) ≥50% leg pain relief at 24 m: 37% vs 2% (p<0.01)	At 6 m SCS patients experienced lower levels of back pain (DM: -11.0; 99% CI: -25.0 to 3.0; p<0.01) and leg pain (DM: -26.7; -40.4 to -13.0; p<0.01), enhanced health-related quality of life on seven of the eight dimensions of the SF-36 (p≤0.02), superior function (Oswestry disability index, p<0.01), and greater treatment satisfaction (p<0.01) Analgesic drug intake was similar in both groups, except for anticonvulsants: 26% vs 50% (p=0.02) Main non-drug therapy	• Only patients experiencing ≥ 80% overlap of their pain with stimulation-induced paresthesia and ≥50% leg pain relief received SCS. Nine patients failed this trial, of whom 5 requested and received SCS anyway • Unblinded study • The SCS patients had more back pain at baseline. p-values were adjusted for base-line values and covariates. Unadjusted p-

Study	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results other relevant outcome(s)	Critical appraisal of study quality
		operate the SCS system; history of a coagulation disorder, lupus erythematosus, diabetic neuropathy, rheumatoid arthritis, or ankylosing spondylitis; active psychiatric disorder, another; life expectancy <1 y; existing or planned pregnancy • Patient characteristics: 51% male			was similar in both groups except for massage and TENS (p≤0.05) More SCS patients were satisfied with pain relief and agreed with their treatment (p<0.01) Rates of return to work did not differ between the groups: 11% vs 3% (p = 0.36). Of 84 patients who received an electrode (either during the screening trial or as a result of system implantation) during 12 m, 27 (32%) experienced a total of 40 device-related complications. For 20 patients (24%), surgery was required. Principal complications were electrode migration (10%), infection or wound breakdown (8%), and loss of paresthesia (7%). In total, 18 (35%) of the SCS group and 25 (52%) of the CMM	values, calculated by us, were similar • Low and non-differential loss to follow up • Cross-over was allowed after 6 m • ITT analysis. Cross-overs were considered treatment failures for the primary outcome at 24 m • Adverse events at 24 m differ between publications. Data given in Kumar 2007 are given here

Study	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results other relevant outcome(s)	Critical appraisal of study quality
					group experienced one or more non-device-related events, most commonly a drug adverse event or development of a new illness, injury, or condition	

Abbreviations: DM: difference in means; ITT: intention to treat analysis; m: months; RCT: randomised controlled trial; SCS: spinal cord stimulation; SD: standard deviation; TENS: transcutaneous electrical nerve stimulation; y: years; VAS: visual analogue score

Table 34 – GRADE assessment of the outcomes of two RCTs on spinal cord stimulation in patients with failed back surgery syndrome

- Outcome - p-value - GRADE - Time point	Crossover	≥50% pain relief and treatment satisfaction	Stable or decreased opioid use	≥50% leg pain relief
SCS vs repeated lumbosacral spine surgery				
North 2005[39]	5 vs 14 p=0.02 LOW -1 study design# -1 imprecision$ 3 years	47% vs 12% p<0.01 LOW -1 study design# -1 imprecision$ 3 years	87% vs 57% p=0.025 LOW -1 study design# -1 imprecision$ 3 years	-
SCS vs CMM				
Kumar 2007[84, 85]	-	-	-	48% vs 9% p<0.01 LOW -1 study design# -1 imprecision$ 6 months
				37% vs 2% p<0.01 LOW -1 study design# -1 imprecision$ 24 months

#: Participants, personnel nor outcome assessors were blinded
$: 50 or 100 participants included

Table 35 – Evidence table of two systematic reviews on spinal cord stimulation in patients with critical limb ischemia

Study	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results other relevant outcome(s)	Critical appraisal of study quality
Klomp 2009[56]	• Systematic review with meta-analysis • Source of funding: Dutch Health Insurance Council • Search date: not reported • Searched databases: Medline, Google, registers of controlled trials • Included study designs: RCTs • Number of included studies: 5	• Eligibility: inoperable critical limb ischemia	SCS with or without conservative treatment vs conservative treatment	Risk ratio mortality: 0.92 (CI: 0.64 to 1.34, 5 studies) Risk difference amputation incidence at 12 m: -0.07 (-0.17 to 0.03, 5 studies)	-	• There was no a priori design provided for this review • Patients with Buerger's disease included in 1 RCT were included • All included studies were non-blinded • Same RCTs included as in Ubbink 2005-2009 • No list of included and excluded studies provided • Quality assessment not reported per item • Study and patients characteristics not described • Publication bias not assessed
Ubbink 2005-2009[57, 58]	• Systematic review with meta-analysis • Source of funding: not reported • Search date:	• Eligibility: inoperable chronic critical leg ischemia; age ≥18 y • Exclusion: leg	SCS with or without conservative treatment vs conservative treatment (best medical therapy,	Risk difference amputations: -0.11 (CI: -0.20 to -0.02, 6 studies) Risk difference amputations RCTs	Adverse effects: • Implantation problems: 9% (CI: 4-15%) • Changes in stimulation requiring	• In 1 RCT 11 patients with Buerger's disease were also enrolled. These 11 patients were

Study	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results other relevant outcome(s)	Critical appraisal of study quality
	September 2008 • Searched databases: Cochrane Peripheral Vascular Diseases Group Specialised Register (including MEDLINE, EMBASE, CINAHL, AMED and hand searching) and the Cochrane Central Register of Controlled Trials (CENTRAL) • Included study designs: 5 RCTs and 1 CT • Number of included studies: 6	ischemia solely due to non-atherosclerotic vascular diseases, like Raynaud's disease or Buerger's disease (no CTs or RCTs were excluded for this reason)	conservative medical therapy, oral analgesics, prostaglandins)	only: -0.09 (-0.19 to 0.01, 5 studies) Risk difference reaching Fontaine stage II: 0.33 (0.19 to 0.47, 2 studies) Risk difference reaching Fontaine stage III: 0.07 (-0.24 to 0.38, 2 studies) NNT to improve one patient to claudication: 3 (CI: 2-5) Mean difference Nottingham health profile: 1 (-0.2 to 2.2, 1 study) Mean difference local transcutaneous oxygen tension: 1.39 (-15.66 to 18.44, 2 studies)	re-intervention: 15% (CI: 10-20%) • Infections of the lead or pulse generator pocket: 3% (CI: 0-6%) • Overall risk of complications with additional SCS treatment: 17% (CI: 12-22%) • Number needed to harm: 6 (CI: 5-8)	excluded from the limb salvage meta-analysis • No description of the treatment allocation process in the 1 included CT • The 1 CT was only included in meta-analysis of limb amputations and adverse effects • All meta-analysis outcomes reported were at 12 m • All included studies were non-blinded • Funding was a predetermined item in the data collection but was not reported on • Publication bias was not assessed. Authors stated that: ´ The chance of publication bias is regarded as small, considering that the manufacturers of

Study	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results other relevant outcome(s)	Critical appraisal of study quality
						nearly all SCS devices are keeping track of all studies that are or have been performed on SCS in this patient group´. This thus not preclude the missing of non-published studies with negative results, however • There were discrepancies between the text and the ´data and analysis´ section, concerning the risk difference for ulcer healing. In the text it was stated that: ´Pooling resulted in no significant difference between the two treatment modalities´ and ´Overall, no significantly different effect on ulcer healing was observed with the

Study	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results other relevant outcome(s)	Critical appraisal of study quality
						two treatments´. In contrast, the risk difference reported in the ´data and analysis section´ was: -0.54 (-0.73 to -0.35, 2 studies)

Abbreviations: CI: confidence interval; CT: controlled trial; m: months; NNT: number needed to treat; RCT: randomised controlled trial; SCS: spinal cord stimulation; TcpO2: transcutaneous oximetry; y: years; VAS: visual analogue score

Table 36 – GRADE assessment of the outcomes of two systematic reviews on spinal cord stimulation in patients with critical leg ischemia

- GRADE - Meta-analysis result - (CI or p-value) - no. RCTs included in meta-analysis - no. patients included in meta-analysis	Mortality	Amputation incidence	Reaching Fontaine stage II	Reaching Fontaine stage III	Nottingham health health profile
Klomp 2009[56]	RR 0.92 0.64 to 1.34 LOW* -1 study design# -1 imprecision† 5 332	RD -0.07 -0.17 to 0.03 LOW* -1 study design# -1 imprecision† 5 332	-	-	-
Ubbink 2005-2009[57, 58]	-	RD -0.09§ -0.19 to 0.01 LOW* -1 study design$ -1 imprecision† 5 321	RD 0.33 0.19 to 0.47 LOW* -1 study design$ -1 imprecision† 2 124	RD 0.07 -0.24 to 0.38 VERY LOW* -1 study design$ -2 imprecision£ 2 206	MD 1 -0.2 to 2.2 LOW* -1 study design$ -1 imprecision® 1 85

**: Publication bias was not assessed in either review*
#: The risk of bias was categorised as ´low´ for one study (all criteria met); ´moderate´ for two studies (one or more criteria met) and ´high´ for two studies (no criteria met). Criteria for risk of bias were: report of settings and locations where the data were collected and dates defining the period of recruitment, randomization, concealment of allocation and completeness of accrual and follow-up
†: Small number of events, optimal information size not met[185]
$: Participants, personnel nor outcome assessors were blinded in any of the studies
£: Small number of events and confidence interval indicates both an appreciable benefit and an appreciable harm
§: Meta-analysis result for RCTs only
®: Small number of events. Scale runs from 1 to 100, so both -0.2 and 2.2 can be seen as a marginal or null effect
Abbreviations: MD: mean difference; RD: risk difference; RR: risk ratio

Table 37 – Evidence table of one RCT on intrathecal analgesic delivery pumps

Study	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results other relevant outcome(s)	Critical appraisal of study quality
Smith 2002[95]	• Design: RCT • Funding: in part by Medtronic Inc. • Setting: multicenter, worldwide • Sample size: n=200 • Duration: April 1999-August 2001	• Eligibility: patients with a documented average pain VAS≥50 mm at two measurements within a week of randomization, despite 200 mg/day of oral morphine or equivalent, or lower doses if opioid side effects refractory to conservative treatment and severe enough to prevent upward titration were present; advanced cancer; pain expected to continue throughout life; age≥18 years; expected life span ≥3 months; suitable	IADP (starting with morphine) + comprehensive medical management vs comprehensive medical management	VAS pain reduced by ≥20% regardless of increased toxicity, or equal VAS with ≥20% reduction in toxicity: 84.5% vs 70.8% (p=0.05) Both pain and toxicity reduced by ≥20%: 57.7% vs 37.5% (p=0.02) Neither pain nor toxicity reduced by ≥20%: 11.3 vs 23.6 (p=0.05)	Serious adverse events: 51 vs 49% (ns) In 8 cases pump revision or explantation was necessary	• Non-blinded study • Differential loss to follow-up: 12 vs 1; differential mortality: 8 vs 15 • Crossover for clinical failure was allowed • Short follow-up (4 weeks) • 22% of patients assigned to IADP had no pump implanted • Data were analysed as randomised • Differences in changes in within-group scores not reported here • The terms ´intrathecal´ and ´intraspinal´ were used interchangeably

Study	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results other relevant outcome(s)	Critical appraisal of study quality
		for IADP • Exclusion: not reported • Patient characteristics: 55% male;				

Abbreviations: IADP: intrathecal analgesic delivery pump; ns: not significant; RCT: randomised controlled trial; VAS: visual analogue score

Table 38 – GRADE assessment of the outcomes of one RCT on intrathecal analgesic delivery pumps

- Outcome - p-value - GRADE - Time point	VAS pain reduced by ≥20% regardless of increased toxicity, or equal VAS with ≥20% reduction in toxicity	Both pain and toxicity reduced by ≥20%	Neither pain nor toxicity reduced by ≥20%	Serious adverse events
Smith 2002[95]	84.5% vs 70.8% p=0.05 LOW -1 study design# -1 imprecision† 4 weeks	57.7% vs 37.5% p=0.02 LOW -1 study design# -1 imprecision† 4 weeks	11.3 vs 23.6 p=0.05 MODERATE -1 study design# 4 weeks	51% vs 49% not significant LOW -1 study design# -1 imprecision† 4 weeks

 # : Participants, personnel nor outcome assessors were blinded. In addition, there was differential loss to follow-up and the study was industry sponsored
†: Optimal information size not met[185]

3.4. Additional searches for non-interventional evidence

3.4.1. Additional searches in Pubmed using Medline

Pubmed was searched on July 3rd 2012.

Limits: published from 2011 onwards, in Dutch, English, French, German or Spanish

("Electric Stimulation Therapy"[Mesh] OR "Infusion Pumps, Implantable"[Mesh] OR "Spinal Cord/therapy"[Mesh] OR neuromodulat* OR SCS OR IADP OR (spinal AND cord AND stimulation) OR (intrathecal AND analgesic AND drug AND pump) OR (intrathecal AND (analgesic OR morphine OR morfine OR drug) AND pump))

AND

("Chronic Pain"[Mesh] OR "Pain, Intractable"[Mesh] OR "Neuralgia"[Mesh] OR "Failed Back Surgery Syndrome"[Mesh] OR "Low Back Pain"[Mesh] OR ("Pain/prevention and control"[Mesh] AND chronic) OR ((chronic OR refractory OR intractable OR persist*) AND pain) OR "Peripheral Vascular Diseases"[Mesh] OR "Thromboangiitis Obliterans"[Mesh] OR critical limb ischaemia OR critical limb ischemia OR buergers disease OR buerger disease OR buerger´s disease OR raynaud disease OR raynauds disease OR "Polyneuropathies"[Mesh] OR polyneuropath* OR (angina AND (refractory OR intractable OR persist*)) OR "Coronary Vasospasm"[Mesh] or vasospas*)

This search yielded 487 hits. Sifting based on title and abstract further reduced this to 112 reference.

3.4.2. Hand searching of four selected journals

We additionally searched the table of contents of the 2011 and 2012 editions of four selected journals and retrieved an additional 105 references and articles based on title and abstract.

- Eur J Pain: 5;
- Pain: 27;
- Neuromodulation: 41;
- Pain Practice: 32.

To these we added the complete series (26) of the EBM guidelinesseries that appeared in Pain Practice since mid 2009.

3.4.3. Update search through Cochrane Library

An update search using the search terms as described in 3.2.3 but extended until July 3rd 2012 yielded no additional relevant reviews or HTAs.

3.4.4. Removal of duplicates

After removal of duplicates we added 207 potentially relevant references.

4. APPENDIX TO CHAPTER ON ECONOMIC EVALUATION

4.1. Search strategies

Project number	2010-13
Project name	HTA Spinal Cord Stimulation
Search question(s)	Is spinal cord stimulation therapy or are intrathecal analgesic delivery pumps cost-effective in treating chronic pain?
Structured search question(s) (PICO, SPICE, ECLIPSE, ..)	*and related keywords*
P (patient)	Patients suffering from chronic pain
I (Intervention)	Spinal Cord Stimulation or Intrathecal analgesic delivery pumps
C (comparison)	Any
O (outcome)	NA

Date	18/06/2012
Database (name + access ; e.g.: Medline OVID)	Medline OVID
Search Strategy	1 exp Electric Stimulation Therapy/ (52689) 2 exp Spinal Cord/ (75137) 3 exp Spinal Cord/th [Therapy] (1) 4 exp Infusion Pumps, Implantable/ (2960) 5 exp Electrodes, Implanted/ (29756) 6 spinal cord stimulation.mp. (1368) 7 (intrathecal and analgesic* and drug* and pump*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (159) 8 IADP.mp. (7) 9 SCS.mp. (2956) 10 (analgesic or morphine or morfine or drug).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (1656580) 11 intrathecal.mp. (14550) 12 pump.mp. (56654) 13 10 and 11 and 12 (314) 14 1 or 3 or 4 or 5 or 6 or 8 or 9 or 13 (81934) 15 exp Chronic Pain/ (647) 16 exp Pain, Intractable/ (5279) 17 exp Failed Back Surgery Syndrome/ (73) 18 exp Low Back Pain/ (12194) 19 exp Pain/dt, pc [Drug Therapy, Prevention & Control] (73745) 20 (chronic or refractory or intractable or persist*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (1135216) 21 pain.mp. or Pain/ (396495) 22 20 and 21 (76947) 23 exp Peripheral Vascular Diseases/ (41559) 24 (critical and limb and ischaemia).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (648)

25 (critical and limb and ischemia).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (2167)

26 exp Thromboangiitis Obliterans/ (2603)

27 buergers disease.mp. (750)

28 buerger disease.mp. (104)

29 buerger's disease.mp. (750)

30 exp Raynaud Disease/ (5919)

31 raynauds disease.mp. (809)

32 raynaud disease.mp. (5622)

33 exp Polyneuropathies/ (20180)

34 (polyneuropathy or polineuropathies).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (8953)

35 angina.mp. (55970)

36 (refractory or intractable or persist*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (366006)

37 35 and 36 (2725)

38 exp Coronary Vasospasm/ (3233)

39 vasospasm.mp. (10747)

40 chronic.mp. (817125)

41 19 and 40 (10545)

42 exp Neuralgia/ (11308)

43 15 or 16 or 17 or 18 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 37 or 38 or 39 or 41 or 42 (177859)

44 Economics, Pharmaceutical/ or Economics, Medical/ or exp Economics/ or Economics, Nursing/ (457366)

45 exp "Value of Life"/ (5220)

46 exp "Costs and Cost Analysis"/ (165257)

47 budget.mp. or exp Budgets/ (19228)

48 budget$.mp. (20746)

49 exp "Cost Control"/ (26644)

50 expend$.mp. (43208)

51 exp Quality-Adjusted Life Years/ (5689)

52 QALY.mp. (3052)

53 (cost analysis or cost analyses).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (41888)

54 (cost-effectiveness or cost effectiveness).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (27517)

55 (cost-utility or cost utility).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (1874)

56 (cost benefit or cost-benefit).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (57208)

57 (cost minimisation or cost-minimisation).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease

	supplementary concept, unique identifier] (169) 58 (price or prices or pricing).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (19448) 59 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 (509477) 60 14 and 43 and 59 (107)
Note	
Date	20/06/2012
Database (name + access ; e.g.: Medline OVID)	EMBASE
Search Strategy	'electrostimulation'/exp AND [embase]/lim OR 400 20 Jun 2012 ('infusion pump'/exp AND [embase]/lim) OR ('spinal cord'/exp AND [embase]/lim) OR (spinal AND cord AND stimulation:ab,ti AND [embase]/lim) OR (neuromodulat* AND [embase]/lim) OR (scs:ab,ti AND [embase]/lim) OR (iadp:ab,ti AND [embase]/lim) OR ('intrathecal'/exp AND analgesic* AND pump* AND [embase]/lim) OR ('intrathecal'/exp AND drug* AND pump* AND [embase]/lim) OR (analgesic* OR 'morphine'/exp OR 'morfine'/exp OR drug* AND 'intrathecal'/exp AND pump*:ab,ti AND [embase]/lim) AND ('chronic pain'/exp/mj AND [embase]/lim OR ('intractable pain'/exp/mj AND [embase]/lim) OR ('neuralgia'/exp AND [embase]/lim) OR ('failed back surgery syndrome'/exp AND [embase]/lim) OR ('low back pain'/exp/mj AND [embase]/lim) OR ('pain'/exp AND chronic:ab,ti AND [embase]/lim) OR ('peripheral vascular disease'/exp/mj AND [embase]/lim) OR (critical AND 'limb'/exp AND ischaemia:ab,ti AND [embase]/lim) OR (critical AND 'limb'/exp AND ischemia:ab,ti AND [embase]/lim) OR ('buerger disease'/exp AND [embase]/lim) OR (buerger OR buerger* AND disease:ab,ti AND [embase]/lim) OR (raynaud OR raynaud* AND disease:ab,ti AND [embase]/lim) OR ('polyneuropathy'/exp/mj AND [embase]/lim) OR (polyneuropath*:ab,ti AND [embase]/lim) OR (refractory OR intractable OR persist*:ab,ti AND angina:ab,ti AND [embase]/lim) OR (vasospasm*:ab,ti AND [embase]/lim) OR ('coronary artery spasm'/exp AND [embase]/lim) OR (chronic OR refractory OR intractable OR persist*:ab,ti AND pain:ab,ti AND [embase]/lim)) AND ('health economics'/exp/mj AND [embase]/lim OR ('health care cost'/exp/mj AND [embase]/lim) OR ('value of life'/exp AND [embase]/lim) OR ('quality adjusted life year'/exp AND [embase]/lim) OR ('cost'/exp AND 'analysis'/exp OR 'cost analysis':ab,ti AND [embase]/lim) OR ('cost'/exp AND effectiveness OR 'cost effectiveness':ab,ti AND [embase]/lim) OR

	('cost'/exp AND effective OR 'cost effective':ab,ti AND [embase]/lim) OR ('cost'/exp AND utility OR 'cost utility':ab,ti AND [embase]/lim) OR ('cost'/exp AND benefit OR 'cost benefit':ab,ti AND [embase]/lim) OR ('cost'/exp AND minimization OR 'cost minimization':ab,ti AND [embase]/lim) OR ('cost'/exp AND minimisation OR 'cost minimisation':ab,ti AND [embase]/lim) OR ('cost'/exp OR cost*:ab,ti AND [embase]/lim) OR (financ*:ab,ti AND [embase]/lim) OR (budget*:ab,ti AND [embase]/lim))
Note	

Date	18/06/2012
Database (name + access ; e.g.: Medline OVID)	CDRS
Search Strategy (attention, for PubMed, check « Details »)	#1 MeSH descriptor **Electric Stimulation Therapy** explode all trees #2 MeSH descriptor **Infusion Pumps, Implantable** explode all trees #3 MeSH descriptor **Spinal Cord** explode all trees #4 MeSH descriptor **Infusions, Spinal** explode all trees #5 (#1 OR #2 OR #3 OR #4) #6 cost* #7 pain #8 (#5 AND #6 AND #7)
Note	

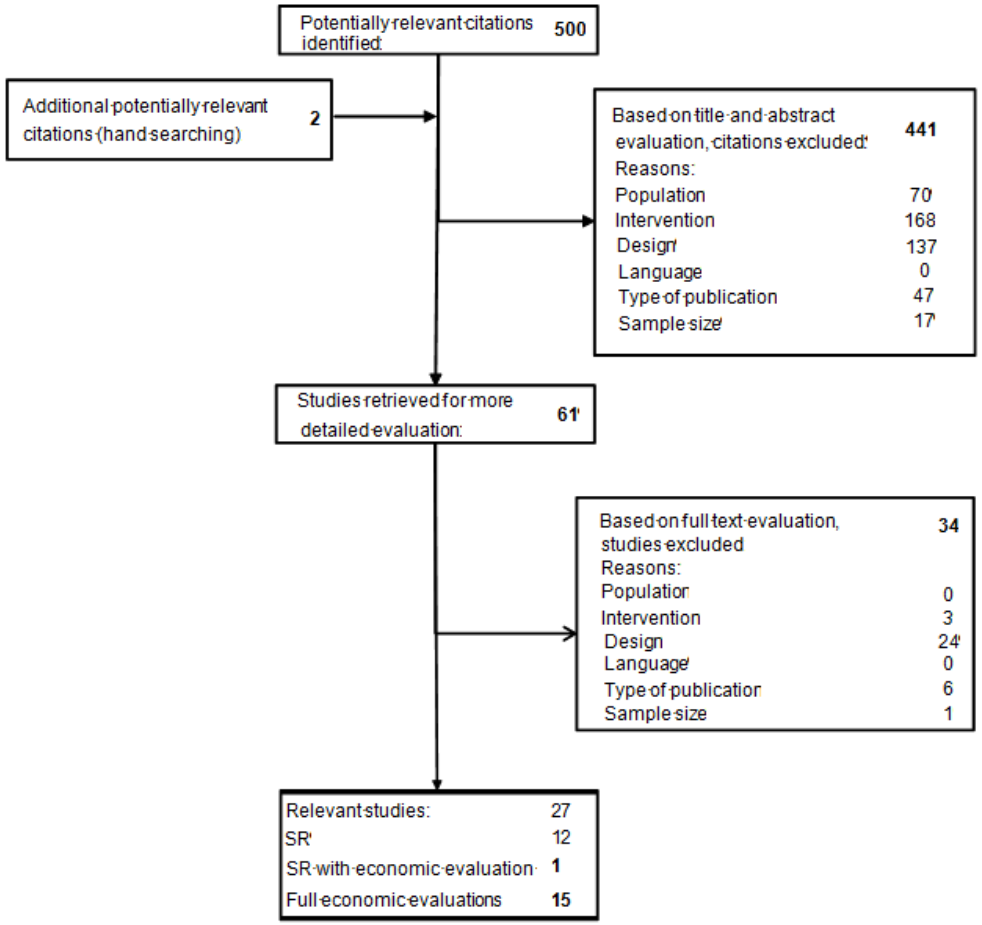
Date	18/06/2012
Database (name + access ; e.g.: Medline OVID)	EconLit
Search Strategy (attention, for PubMed, check « Details »)	1 spinal cord stimulation.mp. 2 spinal cord therapy.mp. 3 spinal.mp. 4 cord.mp. 5 pain.mp. 6 chronic.mp. 7 5 and 6 8 3 and 4 and 7 9 3 and 4 and 5 10 infusion.mp. 11 pump*.mp. 12 10 and 11 13 intrathecal.mp. 14 11 and 13 15 electric stimulation therapy.mp. 16 electric stimulation.mp.
Note	

4.2.

4.3. Literature selection process

An overview of literature selection process is illustrated in Figure 16.

Figure 16 – Flow chart of the literature selection process



Details of costs and outcomes by indication in individual studies

4.3.1. Spinal cord stimulation for FBSS

4.3.1.1. Hollingworth 2011[107]

This recent observational study performed in 158 workers' compensation recipients suffering from FBSS, looked at the cost-effectiveness of SCS versus treating refractory pain patients in a specialised pain clinic or "usual" pain care, over a 24-month period. The most common therapies received under "usual pain care" included physical therapy, back braces/corsets and spinal injections.

The analysis was carried out from a third party payer perspective and included productivity loss costs. Only direct costs were considered. The primary outcome of the study consisted of a composite measure defining success as a reduction in pain ≥50% on a visual analog scale (VAS), a two-point or greater improvement on the Roland Disability Questionnaire (RDQ) and less than daily opioid medication use. Only costs were discounted (at a 3% rate).

The overall results in 2007 US$ showed an adjusted incremental cost per successful outcome with SCS versus usual care of $334 704, while the adjusted ICER of SCS versus treatment at a pain clinic was of $131 146. The authors found no statistically significant differences in productivity costs between the two groups.

Uncertainty was evaluated using a probabilistic sensitivity analysis which showed that SCS was highly unlikely to be the most cost-effective treatment alternative.

The specificity of the population in which the study was performed, the short time horizon used (ie two years) and the small number of patients who completed the study period (43 patients in the SCS arm; 61 patients in the usual care arm and 34 patients treated in a pain clinic), are the main limitations of this study, which was the only one showing negative results for SCS in FBSS patients.

4.3.1.2. Taylor 2010[109]

This economic evaluation used a decision tree and a Markov model to assess the cost-effectiveness of SCS when compared to both conventional medical management (CMM) and re-intervention over a 15-year time period. The extrapolation over this period as opposed to a patient's life time was justified by the authors by the lack of robust outcome data on SCS beyond 15 years. Only direct medical costs were considered and the analysis was performed from a health services perspective. Pain relief, described as an improvement ≥50% on a VAS and QoL, measured via the EQ-5D questionnaire, were the main health outcomes studied. Both costs and outcomes were discounted at a rate of 3,5%. Results in GBP of 2010, showed an ICER of GBP5624 when comparing SCS against CMT and of GBP6392 when comparing it to re-operation.

Probabilistic sensitivity analyses showed that at a threshold of GBP20,000, SCS had a probability of 89% of being cost effective against CMT over a 15-year period, while this was reduced to 82% when compared to re-operation.

An important number of assumptions were made, but were backed up, whenever possible by published literature.

4.3.1.3. Simpson 2009[12]

A two-stage decision analytic model published in 2009 looked at the overall cost-effectiveness of SCS in combination to CMM versus CMM alone and of SCS+CMM versus re-operation in FBSS over a 15-year time horizon. The analysis was carried out from a UK NHS perspective and thus, only medical costs to the health care system were captured in the analysis. Six different health states were described: optimal pain relief (≥50% pain relief on a VAS), with or without complications; sub-optimal pain relief (<50% pain relief on a VAS) with or without complications; no pain relief and death.

Costs and outcomes were discounted at a 3,5% rate.

Clinical data was taken from two main published trials: the PROCESS trial [84] and the trial by North et al. [39]

Costs were converted and presented in GBP of 2007.

The overall results for the base case scenario (15-year time horizon and 4-year lifespan for the IPG battery) show an ICER of GBP 7 996 for SCS in combination with CMM versus CMM alone and an ICER of GBP 7 043 for SCS in combination with CMM versus re-operation.

Although the results reported were positive towards SCS, sensitivity tests varying the lifespan of the IPG battery and the cost of the SCS device show results to be sensitive to both variables.

The main limitation of the model is the amount of assumptions it includes, and the fact that the clinical trials in which it is based are both of a low sample size, industry sponsored and presented no blinding. They also allowed for crossing over from one therapy arm to another. All of these factors make it important to interpret the findings of this study with some caution.

4.3.1.4. Manca 2008[40]

Manca et al performed an economic evaluation alongside a randomised clinical trial in 100 patients aged 18 and over, suffering from predominantly neuropathic pain of radicular origin in the legs. The aim of the study was to compare the cost effectiveness of SCS to that of CMM over a six-month period. CMM included oral medication, nerve blocks, epidural corticosteroids, physical and psychological rehabilitation therapy and chiropractic care.

Only medical costs were included and the primary health outcome captured was HRQoL by means of the EQ-5D. Measurements were made at three and six months. The authors concluded that at six months, SCS offered an improvement on HRQoL of 0.21 when compared to CMM, at an additional cost per patient (in GBP of 2006) of £11 373.

The study had a relatively small sample size and no sensitivity analysis was presented. The authors justified the short time horizon of the study on ethical grounds, since after 6-months patients were allowed to cross-over to the other treatment arm.

4.3.1.5. North 2007[111]

North et al undertook a trial-based economic evaluation in 42 patients characterised by surgically remediable nerve root compression and radicular pain, refractory to conservative care. They aim was to compare SCS to re-intervention. The average follow up period was 3.1 years over which no discounting was performed. Only direct medical costs were included in the calculations and general practice consultations and patients' out-of pocket travel costs were excluded from the analysis. Health outcomes captured during the analysis included frequency of cross over (upon patients' request) and ≥50% pain relief.

Cross-over was allowed (five SCS patients crossed over to re-operation while 13 re-operation patients crossed over to SCS). Results by intent to treat showed SCS to be "dominant". A probabilistic sensitivity analysis resulted in 72% of the simulations falling below the $40 000/QALY. The authors concluded that SCS appeared to be cost-effective when compared to re-intervention in patients suffering from FBSS. Limitations of the study included the very small sample size (SCS=19, re-intervention=21), which did not include all RCT patients but just the first 42 and the use of utility data originating from a study on back pain as opposed to FBSS. These limitations were acknowledged by the authors.

4.3.1.6. Taylor 2005[113]

Taylor et al conducted a cost-utility analysis based on a decision tree and Markov model to compare SCS versus CMM in patients with FBSS over a 2-year period and patients' life time. Only medical costs were taken into consideration and the main health outcome used was a reduction of ≥50% in pain levels, described in the article as "satisfactory pain relief". Utilities for patients with or without satisfactory pain relief and with or without SCS complications were derived from the literature. Costs and outcomes were discounted at a six and 1.5% rate respectively. The battery life for the IPG unit was assumed to be four years for the lifetime calculations.

The authors concluded that SCS was more effective and less costly than CMM over a patient's life time. In the short term, although SCS was potentially cost-effective, the results remained sensitive to some input parameters such as the level of effectiveness.

The study presented a number two main limitations: the method for comparing the effectiveness of SCS and CMM was indirect, and the resource utilisation pattern and costs were taken directly from a Canadian study ([116]), and converted into € (2003 prices) by using European healthcare inflation rates and purchasing parity power, although they were validated by a European expert panel to ensure they were representative of European clinical practice.

4.3.1.7. Blond 2004[114]

In this French, multicentre study a pre and post patient case evaluation was performed, comparing medical costs and outcomes before and after SCS implantation in 43 patients with FBSS who had a confirmed positive response (through a test prior to implantation) to SCS. The study was done over a two-year time period during which discounting was not applied. Resources used prior to implantation were analysed retrospectively. Costs captured included consultations and medical and non-medical pain treatment. Hospitalisation costs were excluded from the calculations.

Both pain relief (≥50% reduction in pain) and HRQoL were considered. The St Antoine and the Oswestry questionnaires were used to capture HRQoL. No discounting was applied to either costs or outcomes. Results showed that successful pain reduction was achieved in 50% of patients at 24 months following SCS implantation (p<0,01). Significant improvement in scores obtained on the St. Antoine and the Oswestry questionnaires were also reported. Total average cost per patient over the study period was reduced by 70,5%. However the exclusion of hospitalisation costs from the calculations may have biased results towards SCS. No sensitivity analysis was undertaken.

4.3.1.8. Kumar 2002[116]

Kumar et al undertook a cost-consequences analysis based on 104 patients with FBSS over a 5-year time frame. Only direct medical costs were captured. QoL, measured through the Oswestry disability questionnaire, and patient satisfaction were analysed. Measurements of QoL were made every year to calculate mean changes over the entire study period. No discounting was applied to either costs or outcomes.

A 27% improvement in QoL with SCS versus 12% for the control arm was reported. Sensitivity tests showed that both the battery and electrode life could have an impact on the overall results.

The average battery life was assumed to be four years, while that of the electrodes was assumed to be five. These assumptions were based on study records. Their results showed the mean cost of SCS over a 5-year period (in CAN$ of 2000) to be CAN$29 123 versus CAN$38 029 for the control arm (p=0.04). A sensitivity test was performed on battery life but only to check what could happen if it improved.

4.3.2. Spinal cord stimulation for CRPS

4.3.2.1. Kemler 2010[108]

This study performed in the UK looked at the cost-utility of SCS in conjunction with CMM versus that of CMM alone in patients aged 18-65 with CRPS and impaired function and symptoms beyond the trauma, with pain affecting one foot or one hand for over six consecutive months. It consisted of a decision tree with six mutually exclusive health states and a Markov model looking at 3-month cycles over a 15-year period. The main data sources were two randomised trials[40, 86] and the main health endpoint was achieving optimal pain relief (≥50% reduction in pain), measured on a VAS. Both costs and QALYs were discounted at a 3.5 % rate.

The results of the base case scenario (assuming 4 years for the battery life of the IPG unit) show an ICER for SCS in combination with CMM versus CMM alone of GBP3 562 per QALY gained (in 2008 GBP). The sensitivity tests showed that at a threshold of GBP30 000 there was an 84% probability for SCS to be cost-effective versus CMM alone.

Lack of detailed data on resource use from the study from which the main assumptions were taken forced the authors to use data from a trial on FBSS as opposed to CRPS. Although the modelling exercise was mainly based on assumptions these were well explained and backed up by published studies, whenever possible. Battery life assumptions for the base case scenario were tested during the sensitivity analyses.

4.3.2.2. Simpson 2009[12]

A two-stage decision analytic model published in 2009 looked at the overall cost-effectiveness of SCS in combination to CMM versus CMMM alone and of SCS in combination with CMM versus re-operation in CRPS over a 15 year time horizon. The analysis was carried out from a UK NHS perspective and only medical costs to the health care system were captured in the analysis. Six different health states were described: optimal pain relief (≥50% pain relief on a VAS), with or without complications; sub-optimal pain relief (<50% pain relief on a VAS) with or without complications; no pain relief and death.

Costs and outcomes were discounted at a 3,5% rate.

Clinical data was taken from one published trial by Kelmer et al.[86]

Costs were converted and presented in GBP of 2007.

The overall results for the base case scenario (15-year time horizon and 4-year lifespan for the IPG battery) show an ICER of GBP25 095 for SCS in combination with CMM versus CMM alone.

These results proved to be highly sensitive to both the cost of the device and the lifespan of the IPG battery during sensitivity testing. The results were thus, not robust and relied on the data from just one RCT, non-blinded and performed on just 36 patients.

4.3.2.3. Kemler 2002[87]

A Dutch economic evaluation performed alongside an RCT explored the cost-effectiveness of SCS in combination with physical therapy versus physical therapy alone in 54 patients with chronic Reflex Sympathetic Dystrophy (RSD) of one extremity. The time frame of the study was one year but results were extrapolated over the patient's lifetime. The authors analysed the data from a societal perspective and thus, included not just the costs to the healthcare system but also transport costs and other out of pocket patient costs (captured by means of a diary). Productivity loss was not measured since none of the patients worked before or at the completion of the study. Aside of costs, changes in pain and patient's QoL were also captured throughout the study. The EQ-5D questionnaire was used in six occasions during the first year of the study to capture changes in patient's QoL. Both costs and outcomes were discounted at a 3% rate.

The battery life of the IPG unit was assumed to be 5 years but sensitivity analyses were performed to evaluate the impact of a shorter battery life on the overall results. The results from the base case scenario show a gain in QALYs and a reduction in costs when treating patients with SCS and physical therapy versus treating them with physical therapy alone. The addition or subtraction of non-medical costs did not appear to alter the overall findings and one-way sensitivity tests showed that the results were robust. However, the study had a very low sample size (particularly in the physical therapy only arm: n=18).

4.3.3. Spinal cord stimulation for critical limb ischemia

4.3.3.1. Klomp 2006[112]

Only one study by Klomp et al. published in 2006 looked at the economic impact of SCS in addition to best medical treatment versus best medical treatment alone in 120 patients with critical limb ischemia not suitable for vascular reconstruction. Best medical treatment included: analgesics, antithrombotics and haemorrheologic drugs, local wound care and antibiotics. The analysis was performed from a societal perspective and included patient out of pocket expenses such as travel cost or costs for adaptations in the home. It excluded productivity losses since most patients were retired. The median follow-up time was 2 years and the health outcomes analysed were patient and limb survival. No discounting was applied to either costs or outcomes.

Since no significant differences were found between the two groups in terms of amputations or deaths the analysis focused purely on cost differences, with total costs of treatment over 2 years for the SCS group (in € of 2000) of € 36 600 versus € 28 700 for best medical treatment alone (p=0.009). The authors concluded that there were no economic benefits derived from the addition of SCS to best medical practice in critical limb ischemia. No sensitivity analysis or extrapolation of the costs over a longer time frame than that of the study were performed.

The high mortality rates (23% within the 1st year and 36% within two years) which did not allow for all patients to contribute towards the costs for the overall study period represent an important study limitation.

4.3.4. Spinal cord stimulation for angina pectoris

4.3.4.1. Dyer 2008[110]

This cost-utility analysis performed in the UK compared SCS versus percutaneous myocardial laser revascularization (PMR) in 60 patients suffering from refractory angina over a 2-year period. There was no attempt to extrapolate costs or consequences beyond the 2-year study period and thus, the effect of IPG battery life or long-term complications were not taken into account. Costs analysed included procedural costs, cardiac medication and inpatient and outpatient admissions. The analysis was performed from a national health system perspective. Primary health outcomes studied included exercise treadmill time, angina morbidity and mortality and QoL. QoL was captured by using both the SF-36 and the EQ-5D instruments in addition to the disease specific Seattle Angina questionnaire. Both costs and outcomes were discounted at a 3.5% rate. Cross-over was allowed (two SCS patients crossed over to PMR, while four PMR patients crossed over to SCS). The results (by ITT) showed no statistically significant differences in terms of patient's QoL or any other relevant outcomes, while the cost of SCS appeared to be higher than that of PMR. The sensitivity analysis performed did not dramatically change the overall results.

4.3.4.2. Yu 2004[115]

Yu et al conducted a before and after retrospective analysis of costs and consequences of SCS in 24 Swedish patients suffering from angina pectoris due to coronary artery disease (CAD) but not suitable for coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI). SCS was compared to the medical procedures performed in these same patients during the three years prior to implantation. Only medical costs were considered and the study was undertaken from a health services perspective. Health outcomes captured included frequency of angina attacks, symptom alleviation, reduction in nitroglycerin intake required and overall QoL. Outpatient clinic visits for ordinary cardiac follow-up were not considered in the calculations since they were assumed to be constant before and after SCS implantation. No discounting was performed for either costs or outcomes. Functional level improved from a median Canadian Cardiovascular Society CCS class three to two (p<0,001). Angina attacks were significantly less frequent after implantation (2.3 per week versus 14 per week before implantation (p<0.01).

Overall, 94% of patients (17/19) experienced moderate or large improvements in QoL (p<0.01) and the acute hospital admissions which had increased in the 3 years prior to SCS implantation, decreased thereafter.

The mean cost saving in CAD care after SCS implantation (in € of 2001) was of € 622 per person, per month (€ 7464 per year). However, the cost of SCS related procedures € 10 195 per person during the first year. This translated into an offset of the initial SCS costs after 16 months of SCS treatment. No sensitivity analysis was performed.

The authors concluded that SCS appeared to be effective in improving angina patient's QoL and symptoms, while saving hospital costs. The very low sample size: n=24 with complete follow-up for only 19 patients, represents a significant limitation of this retrospective analysis.

4.3.4.3. Andrell 2003[92]

This Swedish cost-consequences study was performed as follow-up of a randomised open trial [90] comparing SCS versus coronary artery bypass grafting (CABG) in 104 patients with severe angina pectoris and no anticipated prognostic benefit from CABG. The study was done from a health services perspective over a 2-year period and there was not discounting of costs or outcomes. The endpoints included in the analysis were hospitalisation days due to cardiac morbidity or interventions, fatal and non-fatal myocardial infarctions, cerebrovascular events and complications. Cross-over was allowed. Five SCS patients crossed over to CABG, while five crossed over from CABG to SCS. The results by ITT showed no significant differences in health outcomes.

Mean total costs (in € 2000) per patient over the 2-year study period were lower in the SCS group than in the CABG group (€ 16 400 versus € 18 800 respectively) (p<0,01). The authors concluded that SCS was more cost-effective in angina pectoris than CABG in the patient group studied. No sensitivity analysis was performed.

4.3.5. Intrathecal analgesic delivery pumps for FBSS

4.3.5.1. Kumar 2002[117]

This was a Canadian randomised prospective study aimed at exploring the cost effectiveness of IADP when compared to CMM in 67 patients suffering from FBSS. Costs and consequences were studied over a 5-year period from a health services perspective. Only direct medical costs were included in the calculations. Outcomes studied included HRQoL and patient satisfaction. QoL was captured by means of the Oswestry Disability Index (ODI) throughout the study and presented as mean changes over the five years of the study, while a specific questionnaire was used to explore patients' satisfaction. No discounting was applied to either costs or outcomes. Patients in the IADP group achieved a 27% improvement in QoL as measured by the ODI versus a 12% improvement for the CMM group.

Mean annual costs (in CAN$ of 2000) were significantly lower in the IADP group when compared to the CPT group (CAN$5882 versus 7600 respectively). Sensitivity analyses showed that the period to recover the initial investment in IADP could go up from a base case scenario of 28 months to 33 months if the costs of the device went up by 50%. The authors concluded that even in the worst case scenario results were still positive towards using IADP as opposed to CMM.

4.3.5.2. de Lissovoy 1997[118]

This US study looked at the costs and consequences of treating chronic intractable pain due to FBSS with IADP against conventional management (including medical and non-medical therapy). The study was done from a third party payer perspective over five years and used a decision analytic model. Only direct medical costs were taken into consideration. Average monthly costs and costs over the 60-month period were calculated for a base case scenario which reflected the average values found in the published literature for the relevant inputs. Outcomes studied included the rate of excellent to good pain relief and adverse events. No extrapolation above the five year period was performed and QoL was not captured. Costs were discounted at a 5% rate.

Results for the base case scenario show incremental cost of IADP per year of pain relief versus CMM over a 60-month period of $624, but the costing year was not specified.

Overall the results were robust to changes in the underlying model assumptions. The authors concluded that IADP appear to be cost-effective in the management of patients with FBSS when compared with conventional therapy. The model was based on assumptions which were not always well backed up by evidence since this was, especially at the time of publication, very scarce. Data on adverse events studied in cancer patients and not just in FBSS patients were taken as the basis for some of the model assumptions. Costs of alternative therapy were based on anecdotal data and taken as a constant at a rate of US$1 573 per patient per month.

4.4. Data extraction tables – SCS

Table 39 – Hollingworth 2011

1	Reference (including all authors)	Hollingworth W, Turner J, Welton N et al; Cost and cost-effectiveness od spinal cord stimulation (SCS) for failed back surgery syndrome; Spine 2011, 24(36):2076-2083
2	Conflict of interest and/or study funding	Funding from the Washington State Department of Labor and Industries
3	Country	USA
4	Study question	Is SPS cost-effective when compared to treatment in a pain clinic or “usual”care in patients with failed back surgery treatment (FBSS)
5	Type of analysis (analytic technique)	Cost-effectiveness analysis
6	Design	Observational study
7	Population	158 FBSS patients
8	Intervention	SCS
9	Comparator	Treatment in a pain clinic or usual care
10	Time horizon	24 months
11	Discount rate	3% only for costs
12	Perspective	Health care payer
13	Costs	
	• Cost items included	Medical costs: initial SCS procedure, SCS revision, SCS removal, Hospital inpatient costs, Hospital outpatient costs, office visit costs, medication Other costs: productivity loss costs/compensations
	• Measurement of resource use	Captured resources consumed, for 2 years from the start of the study period, from administrative databases
	• Valuation of resource use	Reimbursement rates rather than charges
	• Data sources	Administrative databases from the Washington State worker’s compensation program
	• Currency and cost year	US $ of 2007
14	Outcomes	
	• Endpoints taken into account and/or health states	Composite measure defining success as: a reduction in pain of ≥50% on a visual analog scale (VAS), a two-point or greater improvement on the Roland Disability Questionnaire (RDQ) and less than daily opioid medication use

	• Valuation of health states	Measurements taken 3 times throughout the study period : as 6, 12 and 24 months
	• Treatment effect and Extrapolation	No extrapolation performed. Only results over the 2-year study period are presented
	• Utility assessment (Quality of Life)	Changes in the RDQ scale
	• Data sources for outcomes	Measurements taken during the study period
15	Uncertainty	
	• Scenario analysis	NA
	• Sensitivity analysis	Probabilistic methods used
16	Assumptions	Gamma distribution assumed for costs. No other explicit assumptions made
17	Results	
	• Cost-effectiveness and/or cost-utility (base case)	Adjusted incremental cost per successful outcome with SCS versus usual care= $334,704 $ Adjusted ICER of SCS versus Pain clinic = $131,146 $
	• Scenario analysis	NA
	• Sensitivity analysis	SCS was highly unlikely to be the most cost-effective treatment alternative (<5% probability)
18	Conclusions	SCS is not a cost-effective treatment alternative to pain clinics or and usual care in workers' compensation patients suffering from FBSS
19	Remarks	The baseline characteristics were not the same in the study groups favoring groups other than the SCS but adjustments were performed Observational study in a very specific population (worker's compensation program) - difficult to generalize the overall findings to other populations Relatively small number of patients analysed in the treatment groups (sample size for those who completed the study period: SCS=43 patients, Usual care=61 patients and Pain clinic=34) Results over a 2-year period. May have differed if the calculations had been done over a longer time horizon Very low success rates with SCS reported when compared with other published studies (RCTs)

Table 40 – Kemler 2010

1	Reference (including all authors)	Kemler M A, Raphael J H, Bentley A et al; The cost-effectiveness of spinal cord stimulation for complex regional pain syndrome; Value in Health 2010, 13(6):735-742
2	Conflict of interest and/or study funding	Sponsored by Medtronic Inc
3	Country	UK
4	Study question	Is the addition of spinal cord stimulation (SCS) to conventional management (CMM) of complex regional pain syndrome (CRPS) cost-effective when compared to conventional management alone?
5	Type of analysis (analytic technique)	Cost-utility analysis
6	Design	Decision analytic model: decision tree (6 mutually exclusive health states) and Markov model (3-month cycles over 15 years)
7	Population	Patients aged 18-65 with CRPS, impaired function and symptoms beyond the trauma, with the pain affecting one foot or one hand for over 6 consecutive months
8	Intervention	SCS in addition to conventional pain management
9	Comparator	Conventional pain management
10	Time horizon	15 years
11	Discount rate	Cost and QALYs discounted at a rate of 3,5%
12	Perspective	National Health Service
13	Costs	
	• Cost items included	Test prior to implantation, implantation procedure, re-implantation, removal (when necessary) drug treatment and non-drug pain treatment costs.
	• Measurement of resource use	Bottom-up approach adopted from PROCESS trial
	• Valuation of resource use	UK unit costs from relevant sources and published estimates
	• Data sources	PROCESS trial (international multicentre trial)
	• Currency and cost year	GBP of 2008
14	Outcomes	
	• Endpoints taken into account and/or health states	Optimal pain relief with and without complications
	• Valuation of health states	Optimal" pain relief defined as ≥50% reduction in pain, measured on a visual analog scale (VAS)
	• Treatment effect and Extrapolation	6-month trial results of SCS compared to CMM alone extrapolated to 15 years by

		means of a Markov model
	• Utility assessment (Quality of Life)	QoL based on responses to the EQ-5D questionnaire collected during trial
	• Data sources for outcomes	Pain relief and short-term complications: from one RCT by same main author Data on long-term complications: from 5-year follow-up data from RCT
	• Other aspects	Data for the model gathered from two different clinical trials
15	Uncertainty	
	• Scenario analysis	One-way sensitivity tests performed
	• Sensitivity analysis	Probabilistic sensitivity analysis. Variables tested: clinical success, resource use, complication rate and SCS failure rate overtime.
16	Assumptions	Health states: SCS patients assumed to remain in their health state unless they experienced a complication, moved from optimal to sub-optimal pain relief, moved to no pain relief or died. Battery life: the life of the non-rechargeable unit left to vary between one and 16 years; rechargeable unit: assumed to last on average nine years No disutility for CMM associated complications
17	Results	
	• Cost-effectiveness and/or cost-utility (base case)	ICER: GBP3 562 per QALY when comparing SCS to CMM When battery life is below four years a rechargeable unit is more cost-effective.
	• Scenario analysis	The cost-effectiveness of SCS remained below GBP20 000 per QALY in all one-way sensitivity scenarios tested
	• Sensitivity analysis	At a threshold of GBP30 000 there is an 84% probability for SCS to be cost-effective in CRPS
18	Conclusions	SCS in combination with conventional pain management is cost-effective in patients with CRPS when compared to conventional pain management alone
19	Remarks	Lack of detailed resource use data from the study from which the main assumptions were adopted, obliged the authors to take “resource consumption” from another trial focused on FBSS as opposed to CRPS. Modeling exercise based on assumptions but these were back up by published studies (mainly two RCTs one for assumptions on resource consumption and one for assumptions on clinical effectiveness) Modeling done over a 15-year period

		Rechargeable versus non-rechargeable IPG tested Battery life assumptions for base case scenario tested during sensitivity analysis

Table 41 – Taylor 2010

1	Reference (including all authors)	Taylor R S, Ryan J, O'Donnell R et al; The cost-effectiveness of spinal cord stimulation in the treatment of failed back surgery syndrome; Clin J Pain 2010, 26(6):463-469
2	Conflict of interest and/or study funding	Funded by Medtronic Inc
3	Country	USA
4	Study question	Is spinal cord stimulation (SCS) in combination with CMM cost-effective when compared to CMM or re-operation in treating failed back surgery syndrome (FBSS)?
5	Type of analysis (analytic technique)	Cost-utility study
6	Design	Decision tree and Markov model
7	Population	Simulated population of FBSS patients
8	Intervention	SCS
9	Comparator	CMM or re-operation
10	Time horizon	15-years
11	Discount rate	3,5% for both costs and QALYs
12	Perspective	Health care perspective
13	Costs	
	• Cost items included	Screening trial, implantation, removal (of electrodes or implantable pulse generator (IPG)) or re-implantation costs, costs from complications, pharmaceutical pain therapy, non-pharmaceutical pain therapy, costs of re-operation.
	• Measurement of resource use	Resources used from PROCESS trial
	• Valuation of resource use	Market prices and tariff costs
	• Data sources	UK National Health Service reference costs 2003, National tariff 2004 and Medtronic information regarding prices
	• Currency and cost year	GBP 2010
14	Outcomes	

	• Endpoints taken into account and/or health states	Pain relief (improvement of ≥50% on a VAS), complications and QoL
	• Valuation of health states	Six possible health states. Data taken from 6-month RCT: Satisfactory pain relief (improvement of ≥50%) with complications; satisfactory pain relief w/o complications, unsatisfactory pain relief with complications, unsatisfactory pain relief w/o complications, no pain relief or death
	• Treatment effect and Extrapolation	6-month trial data extrapolated over a 15 year period by means of a Markov model
	• Utility assessment (Quality of Life)	EQ-5D responses from patients during the PROCESS trial
	• Data sources for outcomes	Published RCT (PROCESS) on 100 FBSS patients
15	Uncertainty	
	• Scenario analysis	One-way sensitivity analysis, changing the base case of each model input to reflect upper and lower estimates
	• Sensitivity analysis	Probabilistic sensitivity analysis performed on the following variables: clinical success, resource use, complication rate and SCS failure rate over time
16	Assumptions	CMM remains as an adjunct treatment in all arms No complications linked to re-operation Long-term SCS complications occur at a rate of 18% CMM complications have no impact on QoL Average battery life taken as 4 years 5% of patients will undergo a re-operation
17	Results	
	• Cost-effectiveness and/or cost-utility (base case)	ICER of SCS against CMM: GBP5 624 ICER of SCS against re-operation: GBP6 392
	• Scenario analysis	The one way sensitivity analysis demonstrated that the cost-effectiveness of SCS at a threshold of GBP20 000 is robust
	• Sensitivity analysis	Probability of 89% that SCS is cost-effective against CMM at a threshold of GBP20,000, over a 15-year period Probability of 82% that SCS is cost-effective against re-operation at a threshold of GBP20 000, over a 15-year period If battery life is below 4 years (taken as base case scenario) a rechargeable SCS device would be more cost-effective
	• Other aspects	NA

18	Conclusions	SCS together with CMM is cost-effective against CMM or re-operation alone
19	Remarks	An important number of assumptions made but backed up, whenever possible, by published literature. Main limitations recognised by the authors Extrapolation over 15 years justified by the lack of robust outcome data on SCS beyond that time horizon No cross-over allowed Both costs and outcomes were discounted

Table 42 – Simpson 2009

1	Reference (including all authors)	Simpson EL, Duenas A, Holmes MW et al; Spinal cord stimulation for chronic pain of neuropathic or ischaemic origin: systematic review and economic evaluation; Health Technology Assessment 2009, 13(17):1-154
2	Conflict of interest and/or study funding	No competing interests reported for the authors
3	Country	UK
4	Study question	Is spinal cord stimulation (SCS) cost-effective when compared to (CMM) in treating chronic pain?
5	Type of analysis (analytic technique)	Cost-utility study
6	Design	Decision tree and Markov model
7	Population	Simulated population of FBSS and CRPS patients
8	Intervention	SCS
9	Comparator	CMM or re-operation for FBSS and CMM for CRPS
10	Time horizon	15-years
11	Discount rate	3,5% for both costs and QALYs
12	Perspective	Health care perspective
13	Costs	
	• Cost items included	Screening trial, implantation, complications, device explantation and failed trial stimulation, pharmaceutical pain therapy, non-pharmaceutical pain therapy and costs of re-operation.
	• Measurement of resource use	From published literature
	• Valuation of resource use	Unit prices/costs multiplied by volume
	• Data sources	Drug costs: BNF 2007

		GP visits: Department of Health (National schedule of reference costs 2006-2007) Trial simulation, complications and device explanation: from Kumar et al 2006186
	• Currency and cost year	GBP of 2007
14	Outcomes	
	• Endpoints taken into account and/or health states	Pain relief (improvement of ≥50% on a VAS), complications and QoL
	• Valuation of health states	Six possible health states: satisfactory pain relief with complications, satisfactory pain relief w/o complications, suboptimal pain relief with complications, suboptimal pain relief w/o complications, no pain relief or death
	• Treatment effect and Extrapolation	6-month trial data extrapolated over a 15-year period by means of a Markov model
	• Utility assessment (Quality of Life)	EQ-5D responses from patients during the PROCESS trial used for FBSS; for CRPS, utility values derived from McDermott et al 2006123
	• Data sources for outcomes	FBSS: data taken from PROCESS trial84 for SCS versus CMM and from North et al 200539 for SCS versus re-operation CRPS: data from Kemler et al 200086
15	Uncertainty	
	• Scenario analysis	Sensitivity analysis performed varying the following parameters: costs of SCS, costs of CMM and device longevity
	• Sensitivity analysis	Probabilistic sensitivity analyses performed
16	Assumptions	Optimal pain relief defined as ≥50% of pain relief from baseline measured by VAS Drug and non-drug costs or CMM in CRPS assumed to be equivalent to those in FBSS Average battery life taken as 4 years Assumes that patients do not change therapy in the first six months of treatment No patient dies during the first six months of treatment When entering the Markov model patients remain in the same health state they were at the end of the first six months Patients on CMM do not experience neither short nor long-term complications Complication rate for SMS after the first six months, assumed to be of 18% per year. Utility for no pain relief health state assumed to be equal to baseline utility across all patients Cost of device explants assumed to be equivalent to the cost of failed trial

		stimulation Annual withdrawal rate for SCS: 3,24% After year two the cost of CMM remains constant but on year two it decreases by 17,8% with respect to year one Costs of acupuncture equivalent to those of a massage
17	Results	
	• Cost-effectiveness and/or cost-utility (base case)	FBSS: ICER SCS+CMM versus CMM: GBP 7 996 per QALY ICER SCS against re-operation: GBP 7 043 per QALY CRPS: ICER of SCS+CMM versus CMM: GBP 25 095 per QALY
	• Scenario analysis	Sensitivity analyses demonstrated that the overall cost-effectiveness of SCS remains more sensitive to device costs and battery lifespan in CRPS than in FBSS
	• Sensitivity analysis	FBSS: Probability of 99% that SCS+CMM is cost-effective against CMM at a threshold of GBP20 000, over a 15-year period Probability of 100% that SCS is cost-effective against re-operation at a threshold of GBP20 000, over a 15-year period CRPS: Probability of 78% that SCS+CMM is cost-effective against CMM at a threshold of GBP20 000, over a 15-year period
	• Other aspects	NA
18	Conclusions	SCS appears to be cost-effective when compared to CMM or re-operation. ICERs were higher when looking at CRPS. The overall results remained sensitive to changes to the cost of the device and its battery life
19	Remarks	An important number of assumptions made but backed up (whenever possible) by published literature. Main limitations is the assumption linked to the battery life (4 years for the base case which may be slightly optimistic) and the cost of the device. Since these were factors that showed, during sensitivity tests, to have a clear impact on the overall results. Extrapolation over the 15 years based on 6-month trial data Both costs and outcomes were discounted Assumptions made clear and explicit and uncertainty well covered

Table 43 – Dyer 2008

1	Reference (including all authors)	Dyer M T, Goldsmith K A, Khan S N et al; Clinical and cost-effectiveness analysis of an open label, single-centre, randomised trial of spinal cord stimulation (SCS) versus percutaneous myocardial laser revascularization (PMR) in patients with refractory angina pectoris: The SPiRiT trial, Trials 2008, 9:40
2	Conflict of interest and/or study funding	Sponsored by Medtronic SA
3	Country	UK
4	Study question	Is SCS cost-effective in patients with refractory angina pectoris when compared to PMR?
5	Type of analysis (analytic technique)	Cost utility analysis
6	Design	Cost-utility evaluation alongside RCT
7	Population	60 patients suffering from refractory angina
8	Intervention	SCS; n=34
9	Comparator	PMR; n=34
10	Time horizon	Two years
11	Discount rate	3,5 for both costs and outcomes
12	Perspective	National Health Insurer
13	Costs	
	• Cost items included	Procedural costs; cardiac medication and inpatient or outpatient admissions
	• Measurement of resource use	Units of resources consumed captured during the trial
	• Valuation of resource use	The most appropriate elective inpatient HRGs (Health related groups) costs used to reflect procedural costs Average costs for a cardiac ward bed applied to length of stay captured during the study
	• Data sources	Hospital costs
	• Currency and cost year	GBP of 2005/2006
14	Outcomes	
	• Endpoints taken into account and/or health states	Exercise treadmill time, angina, morbidity/mortality and QoL
	• Valuation of health states	
	• Treatment effect and Extrapolation	Exercise time captured using a modified Bruce Protocol at 24 months post treatment; Angina measured by the Canadian Cardiovascular Society classification

	• Utility assessment (Quality of Life)	QoL measured by means of the SF-36, EQ-5D and the Disease specific Seattle Angina Questionnaire (SAQ)
	• Data sources for outcomes	Captured during clinical trial
	• Other aspects	NA
15	Uncertainty	
	• Scenario analysis	Some scenarios were studied to assess their impact on overall results
	• Sensitivity analysis	The following parameters were looked by means of a one-way sensitive test: Effect of lower capital costs of SCS or more intense use Taking the implantation of SCS out of the operating theatre Combination of 1 and 2 Impact of deaths on results Using the results from the SF-36D for QoL inputs (as opposed to those obtained via the EQ-5D)
16	Assumptions	
17	Results	
	• Cost-effectiveness and/or cost-utility (base case)	No statistically significant differences in QoL
	• Scenario analysis	NA
	• Sensitivity analysis	The sensitivity analysis performed did not dramatically change the overall results
18	Conclusions	Little difference between SCS or PMR with regard to outcomes while SCS is more expensive than PMR.
19	Remarks	Small sample size (n=68) No blinding but difficult because of paraesthesia No extrapolation of costs or consequences above the 2-year study period. The effect of IPG battery life or long-term complications not considered. Cost items and cost valuation well covered

Table 44 – Manca 2008

1	Reference (including all authors)	Manca A, Kumar K, Taylor R S et al, Quality of life, resource consumption and cost of spinal cord stimulation (SCS) versus CMM in neuropathic pain patients with failed back surgery syndrome (PROCESS trial), European Journal of Pain 2008; 12:1047-1058
2	Conflict of interest and/or study funding	Funded by Medtronic Inc
3	Country	Europe, Canada, Australia and Israel
4	Study question	Is spinal cord stimulation (SCS) cost effective when compared to conventional medical management (CMM) in neuropathic pain patients with failed back surgery syndrome (FBSS)?
5	Type of analysis (analytic technique)	Cost-effectiveness study
6	Design	Economic evaluation alongside prospective RCT
7	Population	100 patients over 18 years of age suffering from predominant neuropathic pain of radicular origin in the legs
8	Intervention	SCS; n=52
9	Comparator	CMM defined as: oral medication, nerve blocks, epidural corticosteroids, physical and psychological rehabilitation therapy, chiropractic care; n=48
10	Time horizon	Six months
11	Discount rate	No discounting necessary (6-month trial)
12	Perspective	Health services
13	Costs	
	• Cost items included	Intervention SCS costs: screening (and failed screening) costs, IPG implantation, SCS related complications, IPG reprogramming sessions CMM related costs: Drug and non-drug treatment for pain
	• Measurement of resource use	Resources used per patient recorded during the trial over a 6-month period
	• Valuation of resource use	Detailed units of resources consumed multiplied by market prices using UK and Canadian 2005-2006 data
	• Data sources	Equipment and consumables: manufacturer's list prices Drugs: BNF 2006 and Ontario Ministry of Health 2006 In-patient costs: fully allocated cost figures Non-drug therapies: published tariffs and estimates from the literature
	• Currency and cost year	GBP and CAN$ of 2005-2006
14	Outcomes	

	• Endpoints taken into account and/or health states	HRQoL
	• Valuation of health states	Use of EQ-5D questionaire
	• Treatment effect and Extrapolation	Captured during the trial. No extrapolation performed
	• Utility assessment (Quality of Life)	At baseline, three and six months
	• Data sources for outcomes	Trial records and UK utility weights (Doland 1997, Kind 1999)
15	Uncertainty	
	• Scenario analysis	NA
	• Sensitivity analysis	NA
16	Assumptions	None made explicit. Information used mostly derived from the actual RCT (PROCESS), not model based
17	Results	
	• Cost-effectiveness and/or cost-utility (base case)	6-month mean adjusted incremental costs of SCS over CMM: CAN$15,395, (95%CI 12,990-17,799); GBP11,373 (95%CI 9,513-13,234), p<0.0001 6-month mean adjusted improvement in QoL of SCS versus CMM: 0,23 (95%CI 0.12-0.35) , p<0,001
	• Scenario analysis	NA
	• Sensitivity analysis	NA
18	Conclusions	At six months, SCS offers an improvement in HRQoL of 0.21 in patients with chronic back and leg pain when compared to CMM, at an additional cost per patient of GBP 11,373 (CAN$ 15,395)
19	Remarks	Relatively small sample size No blinding done, although this is difficult due to paraesthesia Very short time frame (6-months only) and no extrapolation performed above the trial period No sensitivity analysis formally presented Multi country study Costs calculated for both the UK and Canada Cost items included in calculations well explained Analysis done by intention to treat

Table 45 – North 2007

1	Reference (including all authors)	North B, Kidd D, Shipley J et al; Spinal cord stimulation versus reoperation for failed back surgery syndrome: A cost effectiveness and cost utility analysis based on a Randomised, Controlled Trial; Neurosurgery, 2007; 61(2):361-368
2	Conflict of interest and/or study funding	Supported in part by Medtronic Inc
3	Country	USA
4	Study question	Is spinal cord stimulation (SCS) cost-effective when compared to re-operation in patients with failed back surgery syndrome (FBSS)?
5	Type of analysis (analytic technique)	Cost-effectiveness and cost-utility
6	Design	Randomised controlled trial
7	Population	42 patients with FBSS characterised by surgically remediable nerve root compression and radicular pain refractory to conservative care
8	Intervention	SCS; n=19
9	Comparator	Re-operation; n=21
10	Time horizon	Mean follow up from randomization 3,1 years (range 1,6-4,7) (no apriori explanation of the follow-up period)
11	Discount rate	No mention of discounting
12	Perspective	Hospital health services
13	Costs	
	• Cost items included	Hospitalisation related costs: admission, room, operating room, pharmacy, radiology, laboratory, medical and surgical supplies; physical, occupations and respiratory therapy; and other charges such as blood , anaesthesia, etc. Family physician consultations, patient travel costs and indirect costs excluded from the study
	• Measurement of resource use	Economic data collection performed within RCT
	• Valuation of resource use	Costs and charges applied to resources/services used per patient
	• Data sources	Johns Hopkins Hospital billing department for hospitalisation costs and the Johns Hopkins Pain treatment center for data on professional charges
	• Currency and cost year	US$ of 1991-1995
14	Outcomes	
	• Endpoints taken into account and/or health states	Frequency of cross-over (crossing over understood as treatment failure)

		≥50% pain relief and patient satisfaction after completion of long-term follow-up
	• Valuation of health states	Outcome data (and baseline data) assessed and collected by an impartial third party during trial
	• Treatment effect and Extrapolation	No extrapolation performed
	• Utility assessment (Quality of Life)	Values for treatment success and treatment failure taken from one published study in back pain (not specifically on FBSS)
	• Data sources for outcomes	Clinical trial (first 42 patients from a 50-patient clinical trial enrolled in the economic study)
15	Uncertainty	
	• Scenario analysis	No best and worst scenario analysis performed but results presented in three different ways: “intention to treat”, “ treated as intended” and “final treatment”
	• Sensitivity analysis	Bootstraping: in ITT, 72% of the simulations below $40 000/QALY
16	Assumptions	Patients reached a utility score at the cross-over point and at the end of a follow-up period For ITT: Patients lost to follow-up treated as “failures”
17	Results	
	• Cost-effectiveness and/or cost-utility (base case)	ITT: SCS “dominant”, with incremental costs of -6 629$ (p=0,234) per patient and an incremental gain in QALYs of 0,04 (p=0,660)
	• Scenario analysis	NA
	• Sensitivity analysis	Results positive towards SCS independently of the way in which presented.
	• Other aspects	
18	Conclusions	SCS appears to be more cost-effective than re-operation
19	Remarks	Analysis performed by “intention to treat”, “ treated as intended” and “final treatment” Patient baseline characteristics not significantly different across groups Data collected by a disinterested third party Cost items and sources of costs made explicit Utility data taken from a study on back pain rather than on failed back surgery syndrome Very small sample size (SCS=19, re-operation=21). Not all RCT patients included in cost study, only the first 42. Study may have been underpowered Cross-over allowed so last measurements done do not reflect the original

		randomization. Patients crossing-over were captured as treatment “failures” No extrapolation of costs above the study period No discounting performed ITT results: difference in mean costs between the groups, as well as the mean difference in QALYs, was non-significant. Specific incremental cost-effectiveness and cost-utility results for SCS not given. Generalizability not covered

Table 46 – Data extraction sheet: Klomp 2006

1	Reference (including all authors)	Klomp H M, Steyerberg E W, van Urk H et al.; Spinal cort stimulation is not cost-effective for non-surgical management of critical limb ischaemia; Eur J Vasc Endovasc Surg 2006; 31:500-508
2	Conflict of interest and/or study funding	Dutch Fund for Investigative Medicine (no industry funding reported)
3	Country	Netherlands
4	Study question	Is spinal cord stimulation (SCS) cost-effective in non-surgical management of critical limb ischemia?
5	Type of analysis (analytic technique)	Cost-consequences analysis
6	Design	Randomised clinical trial
7	Population	120 patients with critical limb ischemia non suitable for vascular reconstruction
8	Intervention	SCS (quadripolar led) + best medical treatment
9	Comparator	Best medical treatment alone (analgesics, antithrombotic and haemorrheologic drugs, local wound care and antibiotics, if indicated)
10	Time horizon	Two years
11	Discount rate	Costs not discounted
12	Perspective	Societal
13	Costs	
	• Cost items included	Direct medical costs: in-hospital stay, operative procedures, admission to nursing homes, rehabilitation, medical supplies and equipment, SCS device, outpatient visits, out-of pocket costs Other costs: travel expenses and out of pocket costs on home adaptations Did not include costs caused by loss of productivity or absences from work since most patients were retired

	• Measurement of resource use	Based on recorded resource use by patients for 2 years after randomization
	• Valuation of resource use	Detailed cost analysis performed to identify market prices for each relevant cost item
	• Data sources	Trial records for volume of resources consumed; Hospital charges or department based cost registrations and general market prices for costs
	• Currency and cost year	€ of 1993
14	Outcomes	
	• Endpoints taken into account and/or health states	Patient and limb survival
	• Valuation of health states	Number of deaths and number of amputations during the 2-year follow-up from randomization
	• Treatment effect and Extrapolation	Treatment effect measured during the two years of follow up by recording any amputations or deaths from patients. No extrapolation performed
	• Utility assessment (Quality of Life)	NA
	• Data sources for outcomes	Randomised trial registries
15	Uncertainty	
	• Scenario analysis	Not measured
	• Sensitivity analysis	Not performed
16	Assumptions	No assumptions mentioned
17	Results	
	• Cost-effectiveness and/or cost-utility (base case)	Since there were no significant differences between the two groups in terms of amputations or deaths the analysis focused purely on cost differences: total costs of treatment € 36 600 over two years for the SCS group versus € 28 700 for best medical treatment alone; p=0,009
	• Scenario analysis	NA
	• Sensitivity analysis	NA
18	Conclusions	No clinical benefits derived from the addition of SCS to best medical practice in critical limb ischemia. The cost of the former is considerably more expensive than that of best medical treatment alone
19	Remarks	Underpowered to assess differences in amputation High mortality rates (23% within the 1st year and 36% within two years) did not allow for all patients to contribute towards the costs for the overall study period

Table 47 – Data extraction sheet: Taylor 2005

1	Reference (including all authors)	Taylor R J and Taylor R S; Spinal cord stimulation for failed back surgery syndrome: A decision-analytic model and cost-effectiveness analysis; Int J of Technology Assessment in Health care 2005; 21(3):351-358
2	Conflict of interest and/or study funding	Funded by Medtronic, Europe
3	Country	UK
4	Study question	Is spinal cord stimulation (SCS) cost-effective when compared with nonsurgical CMM in patients with failed back surgery syndrome (FBSS)?
5	Type of analysis (analytic technique)	Cost-utility analysis
6	Design	Decision tree and Markov model
7	Population	Patients with FBSS
8	Intervention	SCS
9	Comparator	CMT
10	Time horizon	At Two years and lifetime
11	Discount rate	For costs: 6% for outcomes: 1,5%
12	Perspective	Health care perspective
13	Costs	
	• Cost items included	Costs of SCS implantation; complications; reimplantation; annual maintenance;
	• Measurement of resource use	Taken from a Canadian study validated by a European clinical reference panel
	• Valuation of resource use	Converted directly from the Canadian study once validated by the experts: SCS costs at two years (base case) € 16 250; CMM costs at two years (base case) € 13 248
	• Data sources	Literature and clinical expert panel
	• Currency and cost year	Converted from Canadian $ of 2000 to 2003 € based on purchasing parity power and EU health care inflation rates
14	Outcomes	
	• Endpoints taken into account and/or health states	Satisfactory pain relief (improvement of ≥50%) with complications; satisfactory pain relief w/o complications, unsatisfactory pain relief with complications and unsatisfactory pain relief w/o complications
	• Valuation of health states	Proportion of patients with satisfactory pain relief at two years taken from two different RCTs (47,4% and 5,8% for SCS and CMT respectively)

	• Treatment effect and Extrapolation	Taken from published RCTs with a follow-up of two years. Extrapolated by use of a Markov model to a lifetime
	• Utility assessment (Quality of Life)	Utilities taken from literature and validated by analyzing individual patient data from an RCT; 0,83 and 0,59 with satisfactory and unsatisfactory pain relief respectively. Utility loss associated with a SCS related complication taken from the literature (-0,05 units)
	• Data sources for outcomes	Published RCTs and SRs
15	Uncertainty	
	• Scenario analysis	Results calculated for best and worst case scenarios
	• Sensitivity analysis	Univariate and multivariate sensitivity analysis performed
16	Assumptions	Probability of survival equivalent in both arms CMT treated patients do not experience complication (probability=0)
17	Results	
	• Cost-effectiveness and/or cost-utility (base case)	ICER € 45 819 per QALY
	• Scenario analysis	Best case: ICER € 30 370 per QALY Worst case: ICER € 63 511 per QALY
	• Sensitivity analysis	One way sensitivity analysis showed the results were sensitive to changes in: the level of SCS effectiveness and SCS annual complication rates
18	Conclusions	SCS is more effective and less costly than CMM over the life time of the patient. In the short term, although SCS is potentially cost-effective the results remain sensitive to some input parameters such as the level of effectiveness
19	Remarks	The method for comparing the effectiveness of SCS and SCS was indirect (reasonable but not ideal because of differences in populations) The costs and resources taken directly from the Canadian study, although validated by a European expert panel, may not be totally representative

Table 48 – Blond 2004

1	Reference (including all authors)	Blond S, Buisset N, Dam Hieu P et al; Évaluation coût-bénéfice du traitement des lombosciatalgies post-opératoires par stimulation médullaire ; Neurochirurgie 2004, 50(4) :443-453
2	Conflict of interest and/or study funding	No mention of funding or conflict of interest but according to acknowledgements the data analysis was performed by an employee of Medtronic France
3	Country	France
4	Study question	Is spinal cord stimulation (SCS) a cost-effective treatment for failed back surgery patients (FBSS)
5	Type of analysis (analytic technique)	Cost consequences analysis
6	Design	Multicentre patient case evaluation: pre and post implantation analysis
7	Population	43 patients with failed back surgery syndrome (FBSS), with confirmed positive responses (via a prior-implantation test) to SCS stimulation
8	Intervention	SCS implantation
9	Comparator	Practice followed prior to implantation
10	Time horizon	Two years
11	Discount rate	No discount performed
12	Perspective	Health services
13	Costs	
	• Cost items included	Pain medication, consultations and non-medical pain treatment
	• Measurement of resource use	Resources used one year before implantation of SCS captured retrospectively Resources consumed captured during test, implantation and after implantation for up to two years (measurements post-implantation taken at six, 12 and 24 months post-implantation).
	• Valuation of resource use	Volume of resources and costs captured during the study
	• Data sources	Pre implantation: based on the medical dossier of the patient, an interview and a ‘diary” filled in by each patient for two or three months prior to SCS implantation
	• Currency and cost year	Currency: €. Year of costing not specified
14	Outcomes	
	• Endpoints taken into account and/or health states	Pain relief, reductions in pain intensity, HRQoL
	• Valuation of health states	Successful pain relief: measured as a reduction of ≥50% in pain intensity on a VAS

	• Treatment effect and Extrapolation	No extrapolation performed over the 2-year study period
	• Utility assessment (Quality of Life)	St. Antoine and the Oswestry questionnaires used to measure HRQoL
	• Data sources for outcomes	Captured prior to and during the study period
15	Uncertainty	
	• Scenario analysis	Not undertaken
	• Sensitivity analysis	Nor performed
16	Assumptions	No explicit assumptions given
17	Results	
	• Cost-effectiveness and/or cost-utility (base case)	Successful pain reduction (≥50% reduction on VAS) achieved by 50% of patients at 24 months p<0,01 Significant improvement in scores obtained on the St. Antoine and the Oswestry questionnaires Total mean cost per patients reduced by 70,5% at end of year two. However no hospitalisation costs included, therefore favoring the implantation of SCS
	• Scenario analysis	NA
	• Sensitivity analysis	NA
18	Conclusions	Initial high costs of SCS implantation in FBSS patients is off-set by a reduction in the cost of associated pain therapy
19	Remarks	Small sample size Patient case evaluation – pre and post intervention Hospital costs not taken into consideration because of the short study period – favoring SCS implantation in the cost evaluation part of the study Two-year analysis and no extrapolation of costs and or outcomes performed No discounting No sensitivity analysis undertaken

Table 49 – Yu 2004

1	Reference (including all authors)	Yu W, Maru F, Edner M et al, Spinal cord stimulation (SCS) for refractory angina pectoris : a retrospective analysis of efficacy and cost-benefit ; Coronary Artery Disease 2004 ; 15(1) : 31-37
2	Conflict of interest and/or study funding	Partly funded by Medtronic Inc
3	Country	Sweden
4	Study question	What are the efficacy and costs of spinal cord stimulation (SCS) for the treatment of refractory angina pectoris
5	Type of analysis (analytic technique)	Cost consequences analysis
6	Design	Retrospective case review
7	Population	24 patients eligible for SCS suffering from angina pectoris due to coronary artery disease (CAD) but not suitable for coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI)
8	Intervention	SCS
9	Comparator	Medical management/procedures undertaken during the three years prior to SCS implantation
10	Time horizon	Patient records analysed for an overall period of 4,5 years (three before implantation and 1,5 after implantation)
11	Discount rate	No discount performed
12	Perspective	Health services
13	Costs	
	• Cost items included	Hospital costs included in-hospital days, surgeons, ward staff, operating theater and X-rays Hospital care, CABG and PCI included into annual costs of CAD; SCS costs included two outpatient visits, additional assessment when needed, implantation, management of complications, device controls and device costs
	• Measurement of resource use	Not much detail given but volume of resources used extracted from patient records
	• Valuation of resource use	Average hospital costs for the period 1999-2002
	• Data sources	Patient hospital records
	• Currency and cost year	€ of 2001 (exchange rate used= 1 EUR = 9,25 SEK)
14	Outcomes	

	• Endpoints taken into account and/or health states	Frequency of angina attacks, symptom alleviation (standard detailed CSS angina class criteria), reduction in doses of nitroglycerin required and overall QoL
	• Valuation of health states	Angina attacks, improvement of symptoms and CSS class from medical records
	• Treatment effect and Extrapolation	Treatment effects not extrapolated. Measurement limited to 1,5 years after implantation. Treatment effect taken from hospital records
	• Utility assessment (Quality of Life)	Subjective impressions from patients captured as: greatly improved, moderately improved, not improved and decreased
	• Data sources for outcomes	Hospital records for all endpoints with the only exception of QoL. The latter was extracted from questionnaires filled in by the patients in the clinic
15	Uncertainty	
	• Scenario analysis	Not performed
	• Sensitivity analysis	Not performed
16	Assumptions	Outpatient clinic visits for ordinary cardiac follow-up considered to be constant before and following SCS treatment and thus not included in the calculations
17	Results	
	• Cost-effectiveness and/or cost-utility (base case)	Functional level improved from a median CCS class three to two (p<0,001). Angina attacks significantly less frequent post-implantation: from a median of 14 to 2,3 per week (p<0,01). 94% of patients (17/19) experience moderate or great improvements in QoL (p<0,01) Acute hospital admissions increased in the three years prior to SCS implantation and decreased thereafter. The mean cost saving in CAD care after SCS implantation was of € 622 per person, per month (€ 7 464 in a year). The cost of SCS related procedures was € 10 195 per person during the first year. This translates into an offset of the SCS costs after 16 months of SCS treatment
	• Scenario analysis	NA
	• Sensitivity analysis	NA
18	Conclusions	SCS appears to be effective in improving angina patient's QoL and symptoms, while saving hospital costs
19	Remarks	Very low sample size: n=24 and complete follow-up only in 19 patients

		Retrospective review of hospital records In the calculations, the authors appear to assume that all SCS related costs will only be met in the first year. Although this is mostly true for initial tests and implantation, costs of complication, repositioning of electrodes and or battery changes are also likely to be required after this initial period. Thus, the calculations are too optimistic. No discounting performed No extrapolation of costs and outcomes above the study period No sensitivity analysis performed

Table 50 – Andrell 2003

1	Reference (including all authors)	Andrell P, Ekre O, Eliasson T et al; Cost-effectiveness of spinal cord stimulation (SCS) versus coronary artery bypass grafting in patients with severe angina pectoris – long-term results from the ESBY study; Cardiology 2003; 99:20-24
2	Conflict of interest and/or study funding	No conflict of interest or funding from industry or any other interested groups reported
3	Country	Sweden
4	Study question	Is spinal cord stimulation (SCS) cost-effective in patients with severe angina pectoris when compared to coronary artery bypass grafting (CABG)?
5	Type of analysis (analytic technique)	Cost-consequences analysis
6	Design	Follow up from a randomised, prospective open comparison (ESBY)
7	Population	104 patients with coronary artery disease, severe angina pectoris, no anticipated prognostic benefit from CABG at increased surgical risk
8	Intervention	SCS, n=53
9	Comparator	CABG, n=51
10	Time horizon	2-year follow-up after implant
11	Discount rate	No discounting
12	Perspective	Health services
13	Costs	
	• Cost items included	Costs of primary intervention, costs of hospital stay during follow-up and cost of interventions due to coronary heart disease
	• Measurement of resource use	No specified
	• Valuation of resource use	Not covered in article

	• Data sources	Not covered in article
	• Currency and cost year	€ of 2000
14	Outcomes	
	• Endpoints taken into account and/or health states	Morbidity: hospitalisation days due to cardiac morbidity or intervention; fatal and non-fatal myocardial infarctions, cerebrovascular events Complications from intervention
	• Valuation of health states	Events recorded during RCT and follow-up
	• Treatment effect and Extrapolation	No extrapolation done above the 2-year period follow-up
	• Utility assessment (Quality of Life)	Not included
	• Data sources for outcomes	Events recorded during the entire follow-up of the ESBY trial (2 years)
15	Uncertainty	
	• Scenario analysis	NA
	• Sensitivity analysis	NA
16	Assumptions	None made explicit
17	Results	
	• Cost-effectiveness and/or cost-utility (base case)	No significant differences in health outcomes Mean total costs per patient over the two year period lower in the SCS group (€ 16 400 versus € 18 800 for the CABG group); p<0,01
	• Scenario analysis	NA
	• Sensitivity analysis	NA
18	Conclusions	SCS is more cost-effective in angina pectoris than CABG in the patient group studied
19	Remarks	Data analysed on an ITT basis Small sample size Clinicians not blinded Sources for data on costs or explanation on how resource use was captured and used for the calculation, not provided No sensitivity analysis performed

Table 51 – Kemler 2002

1	Reference (including all authors)	Kemler M A and Furnée C A; Economic evaluation of spinal cord stimulation for chronic reflex sympathetic dystrophy; Neurology 2002, 59:1203-1209
2	Conflict of interest and/or study funding	Grant from the Dutch Health Insurance Council
3	Country	The Netherlands
4	Study question	Is spinal cord stimulation (SCS) in combination with physical therapy (PT) cost-effective when compared to PT alone in the treatment of chronic reflex sympathetic dystrophy (CRPS type I)?
5	Type of analysis (analytic technique)	Economic evaluation alongside RCT
6	Design	Cost-effectiveness and cost-utility analyses
7	Population	54 patients with chronic RSD of one extremity between 18 and 65 years of age
8	Intervention	SCS in combination with physical therapy (n=36)
9	Comparator	Physical therapy alone (n=18)
10	Time horizon	One year, extrapolated to life time
11	Discount rate	At the end of the year: 3% for both costs and outcomes
12	Perspective	Societal
13	Costs	
	• Cost items included	Medical care: SCS costs (1st implant, complications and replacement costs), hospital treatments, GP visits, outpatient visits and bed days Physical therapy costs: disregarded since they were equally generated in both arms Transport costs Out of pocket costs Opportunity costs: disregarded Hours of work lost: not considered (none of the patients worked before or at the completion of the study)
	• Measurement of resource use	Microcosting exercise during trial period
	• Valuation of resource use	Each resource used was captured during the trial period (one year) and then multiplied by the unit price of the service For transport: € 0;27/km
	• Data sources	Financial and service data used obtained from the authorities Cost diaries for out of pocket expenses

	• Currency and cost year	Calculated in Dutch guilders but shown in € of 1998
14	Outcomes	
	• Endpoints taken into account and/or health states	Changes in pain and QoL
	• Valuation of health states	Assessed in multiple occasions throughout the 1st year by means of the EQ-5D for QoL and VAS for pain levels
	• Treatment effect and Extrapolation	Clinical trial results after one year extrapolated to a life time
	• Utility assessment (Quality of Life)	EQ-5D
	• Data sources for outcomes	Clinical trial results after one year
15	Uncertainty	
	• Scenario analysis	Worst case scenario (one year life battery), other tested by way of one-way sensitivity tests
	• Sensitivity analysis	Implemented for the following factors: Discount rate: 0 or 10% Complication rate: 5-% Longevity of battery: 1, 2 or 7 years Life expectancy: 2, 3 or 50 years Implantation rate: 100% Reduction of routine RSD costs (0, 40 or 50%)
16	Assumptions	Assumptions for base case scenario based on results from the trial validated by the published literature Implantation rate: 67% Life expectancy: 40 years Battery life=5 years Complication rate=30%
17	Results	
	• Cost-effectiveness and/or cost-utility (base case)	Incremental costs: € -17 927; Gained QALYs: 2,33. SCS dominates
	• Scenario analysis	Worst case scenario (1 year battery life) still showed an ICER of € 9,352 for SCS in this patient population
	• Sensitivity analysis	One-way sensitivity analysis showed all scenarios tested to be positive towards SCS

	• Other aspects	NA
18	Conclusions	SCS is more effective and less expensive when compared with usual care in patients with chronic RSD
19	Remarks	Appropriate randomization performed but very low sample size (particularly in PT: n=18) No blinding performed, although blinding difficult because of paraesthesia Cost items well explained but no opportunity costs taken into consideration (assumed to be equal for both groups) Life time costs extrapolated from one year data obtained via the study Assumption for battery life for base case (5 years) optimistic when compared to other published literature but the sensitivity analysis showed that even if this was dramatically reduced to one year the results would still be positive towards SCS Frequent measurements of outcomes

Table 52 – Kumar 2002

1	Reference (including all authors)	Kumar K, Malik S and Demeria D; Treatment of chronic pain with spinal cord stimulation (SCS) versus alternative therapies: cost-effectiveness analysis; Neurosurgery 2002; 51(1): 106-116
2	Conflict of interest and/or study funding	No external financial help received for project and no conflict of interest reported
3	Country	Canada
4	Study question	Is spinal cord stimulation (SCS) cost-effective in treating chronic pain?
5	Type of analysis (analytic technique)	Cost consequences analysis
6	Design	Case series
7	Population	104 patients with failed back syndrome (FBBS)
8	Intervention	SCS, n=60
9	Comparator	Control defined as patients referred for SCS who did not underwent electrode implantation, n=44
10	Time horizon	Five years
11	Discount rate	No discounting
12	Perspective	Health services
13	Costs	

	• Cost items included	Hardware costs, professional fees, radiology costs, hospital admissions, drugs, nursing fees, electrode or pulse generator replacements and alternative non-pharmacological therapies
	• Measurement of resource use	Chart reviews and follow-up appointments, supplemented by telephone interviews
	• Valuation of resource use	Hospital charges
	• Data sources	Costs of implantable devices: 2 000 Medtronic price list as charged to Canadian hospitals in 2 000 Professional (doctor and surgeon) costs: payment schedule for the Saskatchewan Medical Association of 2 000 Nursing fees: Nursing Union contracts Costs of imaging procedures: finance department of the Regina Health District Hospitalisation costs: $627 per day – exact amount reimbursed to the hospital by the Saskatchewan government in 2 000 Pharmacotherapy: Saskatchewan Health Formulary
	• Currency and cost year	CAN$ of 2000
14	Outcomes	
	• Endpoints taken into account and/or health states	QoL and patient satisfaction
	• Valuation of health states	QoL measured by use of the Oswestry disability questionnaire (ODQ). Satisfaction captured via a separate questionnaire
	• Treatment effect and Extrapolation	Results from the Oswestry disability questionnaire captured at enrolment and every year during the entire follow-up period, after which mean changes in QoL were calculated
	• Utility assessment (Quality of Life)	Main outcome captured by means of the ODQ
	• Data sources for outcomes	Captured during study
15	Uncertainty	
	• Scenario analysis	NA
	• Sensitivity analysis	One-way sensitivity analysis performed by varying the lifetime of both the electrodes and the implanted device. Both appeared to have a potential impact on the overall results
16	Assumptions	Average battery life for the pulse generator assumed to be four years. Electrodes were assumed to last on average five years after which they would require replacement. Both assumptions were based on observations

17	Results	
	• Cost-effectiveness and/or cost-utility (base case)	Mean costs over 5-year period of SCS CAN$29 123 versus CAN$38 029 in the control; p=0.04 27% of improvement in QoL with SCS versus 12% for the control arm
	• Scenario analysis	NA
	• Sensitivity analysis	If the battery life improved the potential savings from SCS would increase
18	Conclusions	Despite the initial high costs SCS can bring cost savings and result in improved QoL for the patients
19	Remarks	Calculations based on case series. No randomization and no blinding done but groups were matched with respect to patient characteristics before enrolment in the study Relatively small sample size No discounting of costs Sensitivity test done on battery life but only to check what could happen if it improved. No robust data on battery life, which seems to be highly dependent on frequency and intensity of use. Cost items included and sources used well specified (both implantation and maintenance costs for the SCS patient group)

4.5. Data extraction tables – IADP

Table 53 – Kumar 2002

1	Reference (including all authors)	Kumar K, Hunter G and Demeria D; Treatment of chronic pain by using intrathecal drug therapy compared with conventional pain therapies: a cost-effectiveness analysis; J Neurosurgery 97:803-810
2	Conflict of interest and/or study funding	No external funding or conflict of interest reported
3	Country	Canada
4	Study question	Is the use of intrathecal drug therapy (IADP) cost-effective when compared to conventional pain therapies (CPT) in treating patients suffering from chronic low back pain caused by failed back surgery (FBSS)?
5	Type of analysis (analytic technique)	Randomised prospective study
6	Design	Cost consequences analysis
7	Population	67 patients suffering from FBSS
8	Intervention	IADP; n=23
9	Comparator	CPT; n=44
10	Time horizon	5-years
11	Discount rate	Not mentioned
12	Perspective	Health Services
13	Costs	
	• Cost items included	Physician visits, procedures performed over the study period, adjunctive therapies, medications and hospitalisations for the treatment of pain In addition for the IADP group costs of implantation, pump accessories, hospital and surgical fees, complications linked to the implantation or the device and the drug used in the pump were also taken into consideration
	• Measurement of resource use	Data on resources used were extracted directly from patients' flow charts
	• Valuation of resource use	Multiplication of volume by fees or prices
	• Data sources	Fees from Regina, Saskatchewan province's fee schedule For the device: manufacturer's price list obtained directly from Medtronics, Canada, for the year 2 000 Resource volume use: from patients'charts Pharmacotherapy: from hospital formulary

	• Currency and cost year	CAN$ of 2 000
	• Other aspects	NA
14	Outcomes	
	• Endpoints taken into account and/or health states	Health related quality of life (HRQoL) and patient satisfaction
	• Valuation of health states	Oswestry Disability Index (ODI) for QoL and a specific questionnaire for patient satisfaction
	• Treatment effect and Extrapolation	No extrapolation done over the study period
	• Utility assessment (Quality of Life)	Average results from ODI Index over the 5-year period
	• Data sources for outcomes	Captured during the study
15	Uncertainty	
	• Scenario analysis	Best and worst scenario analysis performed by using the average costs for patients in the group who did not have complications (best case) and the average cost of those experiencing complications (worst case scenario)
	• Sensitivity analysis	One-way sensitivity analysis performed to test the weight of: Cost of pump Changes in battery life Complications associated with surgery
16	Assumptions	None made explicit. Data taken directly from study
17	Results	
	• Cost-effectiveness and/or cost-utility (base case)	Patients in the IADP group achieved a 27% improvement in QoL as measured by the ODI versus a 12% improvement for the CPT group Mean annual costs were significantly lower in the IADP group when compared to the CPT group (CAN$5,882 versus 7,600 respectively)
	• Scenario analysis	Even in the worse case scenario results were still positive towards using IADP versus CPT
	• Sensitivity analysis	Sensitivity analyses showed that the period to recover the initial investment in IADP could go up from a base case scenario of 28 months to 33 months if the costs of the device went up by 50%
18	Conclusions	In patients who respond to the treatment IADP is cost-effective despite its initial implantation costs when compared to CPT
19	Remarks	Very low sample size (particularly for the IADP group, n=23

		Method of randomization not explained but groups matched at the beginning of the study for patients' characteristics Cost items and cost sources well specified

Table 54 – De Lissovoy 1997

1	Reference (including all authors)	De Lissovoy G, Brown R E, Halpern M et al; Cost-effectiveness of long-term intrathecal morphine therapy (ISDP) for pain associated with failed back surgery syndrome (FBSS); Clinical therapeutics 1997, 19(1):96-112
2	Conflict of interest and/or study funding	Funded by Medtronic Inc
3	Country	USA
4	Study question	What are the costs of intrathecal morphine therapy administered via an implantable pump versus alternative therapies?
5	Type of analysis (analytic technique)	Cost-effectiveness analysis
6	Design	Decision analytic model
7	Population	Simulated cohort of 1000 patients suffering from chronic intractable pain due to FBSS
8	Intervention	Intrathecal morphine via an implantable pump
9	Comparator	Alternative medical management
10	Time horizon	60 months
11	Discount rate	Costs discounted at 5%
12	Perspective	Third party payer
13	Costs	
	• Cost items included	For IADP: Screening evaluation, initial implant, minor complications, major complications, ongoing therapy, pump replacements, explants pump For conventional therapy: Medication, hospital admissions, emergency room visits for breackthrough pain, physician office visits, alternative therapy (passive physical therapy, chiropractic, psychologist/psychiatrist, etc)
	• Measurement of resource use	Average month costs and costs over a 60-month period calculated by the model for a base case scenario reflecting the average values of published literature for all inputs
	• Valuation of resource use	Volume of resources used per year multiplied by the estimated charge per unit
	• Data sources	Drug costs: published wholesaler prices,

		Billing data analysis performed by the authors and hospital discharge data from Florida and Wisconsin
	• Currency and cost year	USA$. Costing year not specified
14	Outcomes	
	• Endpoints taken into account and/or health states	Rate of excellent or good pain relief Adverse events
	• Valuation of health states	Rate of successful pain relief taken from one study, adverse events taken from three studies (not just on FBSS but also on cancer patients)
	• Treatment effect and Extrapolation	No extrapolation done above the five years covered in the model
	• Utility assessment (Quality of Life)	NA
	• Data sources for outcomes	Taken from the scarce literature published at the time of the study
15	Uncertainty	
	• Scenario analysis	Best and worst scenario analysis was performed by taken the worst and best estimates from the published literature. The base case represented mean estimates
	• Sensitivity analysis	To cover for uncertainty the authors independently varied each model input (costs and adverse events) across its low-high range
16	Assumptions	Adverse events assumed to remain constant over a 60 month period Mean % of excellent to good pain relief assumed to be 73%, calculated as an average of published estimates (based on just one study) Patients in the conventional therapy arm 30% retail mark-up for drug prices (estimates based on wholesaler prices) Costs for conventional treatment assumed to be US$1 573 per month Base case failure rate for the battery set at 48 months. Provided by the manufacturer No costs of potential future surgeries included in the 60-month analysis
17	Results	
	• Cost-effectiveness and/or cost-utility (base case)	Base case: incremental cost of IADP per year of pain relief versus conventional treatment over a 60 month period= US$624
	• Scenario analysis	Best case results: incremental cost of IADP per year of pain relief versus conventional treatment over a 60 month period = - US$7832 Worst case results: incremental cost of IADP per year of pain relief versus conventional treatment over a 60 month period US$12276

	• Sensitivity analysis	Overall the results were robust to changes in the underlying model assumptions
18	Conclusions	IADP appear to be cost-effective in the management of patients with FBSS when compared with conventional therapies
19	Remarks	Model based on assumptions not always well backed up by evidence since this was (at the time of publication) very scarce Data on adverse events studies in cancer patients and not just in FBSS patients were taken into consideration as basis for some of the assumptions Model allowed patients to stop IADP at any month and they were then assumed to cross-over to alternative medical treatment Costs of alternative medical therapy based on anecdotal data and taken as constant at a rate of US$1 573 per patient per month Model study period not well justified

5. APPENDIX TO CHAPTER ON BELGIAN REGULATION FOR REIMBURSEMENT

5.1. Overall legal framework for reimbursement of medical acts

The RIZIV–INAMI (NIHDI) nomenclature is based on a Royal Decree issued in September 1984 and starting from 1985-01-01, all codes – listed in an extensive annex - come in a predefined 6-digit format, composed of a 5-digit core number followed by a check-digit in sixth position. Periodical changes and updates, issued by the RIZIV–INAMI Insurance Committee, are ratified by publishing modifications to the above mentoined Royal Decree in the Belgian Official Bulletin (Belgische Staatsblad – Moniteur Belge).

So called 'pseudocodes' are published through periodical circular letters to the national health insurance companies or in specific billing instructions manuals for health care providers ('instruction codes'[a]).

Information included in this appendix was current in 2011. For more recent updates the relevant website of RIZIV–INAMI should be consulted.

5.2. Legal framework for Implantable devices

Chapter IX of the nomenclature annex deals specifically with implantable or invasive devices as opposed to extracorporeal prostheses or devices (Chapter VI, art. 27-31). Article 35 lists by nomenclature number those implants that are within the competence of the implant supplier.[187]

5.2.1. Definition of an implant

"For the application of this law, with 'implant' is understood: every instrument, device, equipment, any substance or any other item, used solely or in combination, including accessories and software necessary for its well functioning and destined by the manufacturer for exclusive human use and mainly for the following purposes:

- Diagnosis, prevention, monitoring, treatment or relief of a disease, wound or disability;
- The study, replacement or modification of the anatomy or physiological process.

and which primary intentioned action on the human body is not entirely pharmacological, chemical, immunological nor metabolic. However, its functioning may well be assisted in this way. The implant is either completely or partially implanted into the human body or a natural orifice by means of a surgical or medical intervention. Alternatively, it may also replace part of an epithelial tissue. It is intended to remain in place after the intervention for at least 30 days. Moreover, the implant can only be removed by means of a surgical or medical intervention."[124]

The above legal definition is in accordance with the definition of *implantable device* as provided by relevant EU Council Directive (in force 20.07.1990),[188] and the amendment Annex IX of the Council Directive 93/42/EEC (in force 12.07.1993).[189]

5.2.2. Belgian categories of implantable devices

Article 35 of R.D. 24.08.1994 also defines a number of implant categories which are listed below. This is of relevance to this HTA because even though most concerned devices are in category 1, some spinal cord stimulators are in category 5.

- Category 1: Active implant.

Any implant that for its functioning depends on an electrical energy source or any other energy source other than generated by the human body or gravity.

- Category 2: High-risk implant.

[a] instructies voor aflevering van facturatiebestanden op magnetische of elektronische drager = IMD; instructions relatives à la facturation sur support magnétique ou éléctronique = ISM)

Any implant intended to replace, modify or assist the essential anatomical-biological function or a vital physiological process.

- Category 3: Implant of moderate or low risk.

Any implant not pertaining to the definitions of the other categories.

- Category 4: Custom-made implant.

Any implant specifically manufactured according to the prescription of an implanting specialist physician, who specifies under his responsibility the design characteristics. The implant is intended to be used with one specific patient.

- Category 5: Implant intended for restricted clinical use

Any implant intended to be put at the disposal of a specialist physician and to be used in an appropriate human clinical environment and/or for specified indication.

R.D. of 24.03.1998 (in force 01.05.1998) further specifies Category 5:

"This concerns:

- Either a new or slightly modified version of a category 1 or 2 implant already included in the limitative lists (see 5.3.2) and this for an approved indication;
- Or an implant of category 1 or 2 already included in the limitative lists and this for a new indication;
- Or a completely new implant for which the Technical Commission for Implants (NIHDI) considers a reimbursement evaluation period necessary."

5.2.3. European classification of medical devices

The above-mentioned Belgian category system should not be confused with the European classification as specified in Annex IX of the Council Directive 93/42/EEC "concerning medical devices".[189] The European classification system divides implantable devices into four classes according to the associated risk: Class I for a low risk, Class IIa for a medium risk, Class IIb for an elevated risk) and Class III for a high risk. A higher classification implies a more elaborate assessment by the notified bodies.

A Notified Body, in the European Union, is an organisation that has been accredited by a Member State to assess whether a product meets certain preordained standards. Assessment can include inspection and examination of a product, its design and manufacture. For example, a Notified Body may certify that a medical device conforms to the EU Medical Devices Directive defining the standards for medical devices. This certification allows the manufacturer to label the product with the CE Mark, which is required for distribution and sale in the EU.

EU member states will then inform the European Commission whether a product complies with set standards or not, and the names of bodies will be disclosed (for more information see http://ec.europa.eu/enterprise).

5.3. Implants concerned by this HTA

5.3.1. Implants by category

The SCS and IADP implants concerned by this HTA are listed by category in Table 55 to Nomenclature numbers beyond data acquisition time-horizon are greyed.

Table 57. The lists are sufficient and limited to identify procedures only related to SCS and IADP. Obviously, more implants may be used during a procedure. For example, cement may be used during the implantation of a laminectomy electrode. Such implants are not listed here because they do not uniquely identify procedures concerned by this HTA. The shaded lines correspond to nomenclature numbers that are too recent to appear in the data set used in chapter 7 - Neuromodulation Use in Belgium. Some words have been emphasised by the authors in order to increase readability.

Table 55 – Implants of category 1 'active implant' concerned by this HTA and related to SCS

nomenclature number			
ambulatory	**hospitalised**	**start date**	**label**
683093	683104	19.10.1994	Implanted neurostimulator, **patient programmer included**
683115	683126	19.10.1994	Implanted electrode and accessories for neurostimulator
683130	683141	19.10.1994	Electrode in case of negative stimulation trial
715094	715105	01.11.2009	Implanted **replacement** neurostimulator, **patient programmer included**
715116	715120	01.11.2009	**First rechargeable** neurostimulator
715131	715142	01.11.2009	**Replacement rechargeable** neurostimulator
715153	715164	01.11.2009	**Premature replacement rechargeable** neurostimulator

Nomenclature numbers beyond data acquisition time-horizon are greyed.

Table 56 – Implants of category 1 'active implant' (Article 35 of R.D. 24.08.1994) concerned by this HTA and related to IADP

nomenclature number			
ambulatory	**hospitalised**	**start date**	**label**
683152	683163	19.10.1994	**Programmable,** electronically controlled implantable **pump** with adjustable flow rate, intended to administer morphine or a morphinomimetic
683196	683200	01.11.2004	Implantable **pump with constant flow rate,** intended to administer morphine or a morphinomimetic
709111	709122	01.08.2010	**Programmable**, electronically controlled implantable **replacement pump** with adjustable flow rate, intended to administer morphine or a morphinomimetic
709155	709166	01.08.2010	Implantable **replacement pump with constant flow rate**, intended to administer morphine or a morphinomimetic
709170	709181	01.08.2010	Catheter and programming accessories for an implantable pump
709192	709203	01.08.2010	Catheter in case of negative trial

Nomenclature numbers beyond data acquisition time-horizon are greyed.

Table 57 – Implants of category 5 'intended for restricted clinical use' concerned by this HTA and related to SCS in case of chronic critical non-operable ischaemia of the lower limbs

nomenclature number			
ambulatory	**hospitalised**	**start date**	**label**
686232	686243	01.04.2001	Implanted neurostimulator
688251	688262	01.04.2001	Replacement in case of end-of-life
688273	688284	01.04.2001	Replacement in case of infection
686254	686265	01.05.2010	Implanted electrode and accessories for neurostimulator
688295	688306	01.05.2010	Implanted electrode and accessories for neurostimulator, replacement in case of end-of-life
688310	688321	01.05.2010	Implanted electrode and accessories for neurostimulator, replacement in case of infection
686276	686280	01.05.2010	Electrode in case of negative stimulation trial

Nomenclature numbers beyond data acquisition time-horizon are greyed.

5.3.2. Description and structure of the limitative lists

The information described below was valid at the time of writing. The most current situation and the full details of the limitative lists can be retrieved from the RIZIV–INAMI website at:

http://riziv.be/care/nl/other/implants/information-topic/listart35_35bis/index.htm

R.D. 24.08.1994 (in force 19.10.1994) and R.D. 25.06.1997 (in force 01.08.1997) states that RIZIV–INAMI is responsible for publishing:

- The lists of implants accepted for reimbursement by the health- and disability insurance, and
- The additions and revisions upon decision by the Insurance Committee.

Implants of category 1 are only considered for reimbursement when they are included in the limitative lists set by the Insurance Committee. The reimbursed amount takes into account the regulations for price fixing established by the Minister responsible for Economic affairs.

As for implants of category 5, it is the Technical Council of Implants that sets the evaluation modalities, reimbursement criteria and the amount covered by the insurance. The Technical Council of Implants presents its proposal to the Agreements Commission implant suppliers - healthcare insurers in order to obtain a recommendation, upon which it is submitted to the Insurance Committee for approval (R.D. 28.02.1999, in force 01.05.1999).

Nine limitative list relevant to this HTA have been identified. These lists contain the price of the specific device, reimbursement amounts, patient supplements and delivery margins.

The nine lists concern:

1. Category 1, concerning nomenclature couples:

- 683093-683104: (Non-rechargeable) implanted neurostimulator, patient programmer included,
- 715094-715105: Implanted replacement (non-rechargeable) neurostimulator, patient programmer included.
- This limitative list comprises (all separately billable):

- Fully implantable systems;
- Partially implantable systems: internal receivers;
- Partially implantable systems: external emitters;
- Partially implantable systems: internal antennas;
- Patient programmers, all priced at € 0.00.

2. Category 1, concerning nomenclature couples::

- 683115-683126: Implanted electrode and accessories for neurostimulator;
- 683130-683141: Electrode in case of negative stimulation trial;
- This limitative list comprises (all separately billable):
  - Extension cables;
  - Different types of electrodes.

3. Category 1, concerning nomenclature couples:

- 715116-715120: First rechargeable neurostimulator;
- 715131-715142: Replacement rechargeable neurostimulator;
- This limitative list comprises (all separately billable):
  - Rechargeable neurostimulators;
  - Chargers.

4. Category 1, concerning the nomenclature couple:

- 683115-683126: Implanted electrode and accessories for neurostimulator. This limitative list contains
  - Electrodes;
  - Patient programmers, all priced at € 602.32.

5. Category 5, in case of chronic critical non-operable ischaemia of the lower limbs and concerning nomenclature couples:

- 686232-686243: Implanted neurostimulator;
- 688251-688262: Replacement in case of end-of-life;
- 688273-688284: Replacement in case of infection;
- This limitative list comprises (all separately billable):
  - Fully implantable systems;
  - Partially implantable systems: internal receivers;
  - Partially implantable systems: external emitters;
  - Partially implantable systems: internal antennas.

6. Category 5, in case of chronic critical non-operable ischaemia of the lower limbs and concerning nomenclature couples:

- 686254-686265: Implanted electrode and accessories for neurostimulator;
- 688295-688306: Implanted electrode and accessories for neurostimulator, replacement in case of end-of-life;
- 688310-688321: Implanted electrode and accessories for neurostimulator, replacement in case of infection;
- 686276-686280: Electrode in case of negative stimulation trial;
- This limitative list comprises (all separately billable):
  - extension cables;
  - different types of electrodes;
  - Accessories being patient programmers, all priced at € 262.77, except one at € 394.15 as well as a programming magnet priced at € 39,42.

7. Category 1, concerning nomenclature couples:

- 683196-683200: Implantable pump with constant flow rate, intended to administer morphine or a morphinomimetic;
- 709155-709166: Implantable replacement pump with constant flow rate, intended to administer morphine or a morphinomimetic.

8. Category 1, concerning nomenclature couples:

- 683152-683163: Programmable, electronically controlled implantable pump with adjustable flow rate, intended to administer morphine or a morphinomimetic;
- 709111-709122: Programmable, electronically controlled implantable replacement pump with adjustable flow rate, intended to administer morphine or a morphinomimetic;

9. Category 1, concerning nomenclature couples:

- Catheter and programming accessories for an implantable pump;

- Catheter in case of negative trial;
- Besides catheters, this list contains patient programmers with prices ranging from € 513.26 to € 746.67.

5.3.3. Warranty periods

The warranty period for rechargeable neurostimulators is nine years: a full warranty of five years followed by a four-year pro rata (of remaining years) warranty. A full warranty of nine years applies to the charge unit. (R.D. 13.06.2010, Art. 35, §7, 11°)

There are currently no warranty provisions for:

- Non-rechargeable, category 1 & category 5 spinal cord stimulators;
- Electrodes;
- Intrathecal analgesic delivery pumps;
- Catheters;
- Other accessories like patient programmers.

However, those regulations for warranty periods are being debated and might change in the future.

5.4. Approved indications, devices and regulations

Following indications can be approved by the advisory physician (R.D. 13.06.2010, Art. 35, §7, 2°, a-d):

5.4.1. Neurogenic pain syndromes

The implantation of:

- Non-rechargeable category 1 spinal cord stimulators (SCS), their electrodes and accessories, as well as
- Programmable and non-programmable intrathecal analgesic delivery pumps (IADPs) and their catheters

needs to be aimed at the treatment by:

- Intracerebral stimulation or;
- Stimulation of the spinal cord or ;
- Intrathecal administration of morphine or morphinomimetics

of long-lasting **neurogenic pain syndromes** originating in

- The central nervous system;
- The spinal cord;
- A spinal nerve root or;
- A traumatic lesion of a peripheral nerve;

that did not respond to surgical and/or pharmacological treatment.

5.4.2. Thromboangiitis obliterans

The implantation of

- Non-rechargeable Category 1 spinal cord stimulators (SCS), their electrodes and accessories

need to be aimed at the treatment of

- Thromboangiitis obliterans (also known as Buerger's disease)

where the patient experiences;

- Ischaemic pains at rest and/or;
- Shows limited trophic disturbances (i.e. skin lesions , ischaemic ulcers).

without an indication for surgical or percutaneous revascularisation or fibrinolysis.

5.4.3. Chronic pancreatitis

The implantation of

- Non-rechargeable Category 1 spinal cord stimulators (SCS), their electrodes and accessories, as well as;
- Programmable and non-programmable intrathecal analgesic delivery pumps (IADPs) and their catheters ;

needs to be aimed at the treatment of

- Pain caused by chronic pancreatitis;

where current pharmacological treatment

- Did not deliver favourable results, or;
- Led to serious adverse effects.

5.4.4. Critical lower limb ischemia

In 2007 a temporary agreement was issued by RIZIV—INAMI in application of R.D. 13.06.2010, Art. 35, §4, 5° (dealing with implants of category 5), to allow reimbursement of SCS for the indication critical lower limb ischemia. The conditions for reimbursement are very strict, is limited to maximum 50 patients each year and reimbursement requires approval by the college of medical directors. This agreement was intended to end by 2012 but has been extended.[a] Is is reported to be used in only a few cases each year.

5.4.5. Rechargeable neurostimulator

The implantation of

- Rechargeable Category 1 spinal cord stimulators (SCS), their electrodes and accessories;

needs to be aimed at the treatment by

- Stimulation of the spinal cord

of long-lasting neurogenic pain syndromes originating in

- The central nervous system;
- The spinal cord;
- A spinal nerve root or;
- A traumatic lesion of a peripheral nerve.

that did not respond to surgical and/or pharmacological treatment.

Entitled are only beneficiaries who already were implanted a non-rechargeable Category 1 spinal cord stimulator that needed replacement due to 'end of (service) life' within two years after implantation.

5.5. Implant suppliers and the delivery margin

5.5.1. National agreement

The Agreements Commission negotiated a national agreement between the implant suppliers and the insurance organisations,[187] aiming at:

- Ensuring the beneficiary tariff surety for the provisions in this agreement by keeping them informed about the prices and reimbursements;
- Guaranteeing the price of the provisions in this agreement for at least a year;
- Eensuring a delivery margins for the hospital pharmacist.

The agreement furthermore requires the implant supplier to:

- Deliver and/or attest the implant;
- Keep the implant prices constant during at least one year;
- Provide tariff lists to the hospital and the potential implanters;
- Perform a limited set of other administrative tasks like printing the code and reference number of the implant on the hospital bill, etc.

Article 35 of the Royal Decree of 24 August 1994 lists by nomenclature number those implants that fall within the competence of the implant supplier.

[a] http://www.belsurg.org/uploaded_pdfs/108/108_139_149.pdf

5.5.2. The delivery margin

The legal requirements concerning the delivery margin of the hospital pharmacist for implants are determined by the Ministerial Ruling of 18 February 1998.

5.6. Approved implanting centres

The legal basis can be found in R.D. 13.06.2010, Art. 35, §7, 3°

5.7. Trial period

The legal basis can be found in R.D. 13.06.2010, Art. 35, §7, 3° & 5°

The trial consist in the stimulation at cerebral or spinal level or the intrathecal administration of morphine or morphinomimetics, **carried out during a time period of minimum four weeks of which at least two weeks extramural, at the patient's normal residence.**

The trial must be evaluated according to standardised criteria and is assessed on the basis of the following elements:

- Pain;
- Medication;
- Daily activities;
- Quality of life.

Evaluation is done twice with mentioning of the dates; once before the trial and a second time at the end of the fourth week. The outcome of the trial is considered positive when **all of the following criteria** are fulfilled:

- A pain reduction of at least 50%;
- A pronounced reduction of the medication (either by reducing doses, by falling back on lighter analgesics or by stopping medication);
- A significant improvement of the scores on 'daily living activities' and 'quality of life';
- For implantations mentioned under Section 5.4.2 (thromboangiitis obliterans): an increase in walking distance;
- For implantations mentioned under Section 5.4.2 (thromboangiitis obliterans): an improvement or healing of the trophic disturbances.

To this end, the Committee of health insurance of RIZIV–INAMI has prepared a form, as proposed by the College of physician-directors.

The electrode or catheter of the trial is reimbursed under the nomenclature couple 683130-683141, respectively 709192-709203, when:

- The trial carried out during at least four weeks turns out negative, and;
- All previously mentioned required reimbursement criteria were met.

These regulations on the trial period are currently being debated and might change in the future.

5.8. Request for reimbursement

The legal basis for reimbursement can be found in R.D. 13.06.2010, Art. 35, §7, 3°.

5.8.1. Requirement of a multidisciplinary team

The request for reimbursement of the material needs to be submitted accompanied by a comprehensive medical report drafted and signed by all members of the multidisciplinary team responsible for the implantation and the treatment, and that comprises:

- For implantations mentioned under Section 5.4.1 (neurogenic pain syndromes); a neurosurgeon, a neurologist or an anaesthetist and a neuropsychiatrist or psychiatrist
- For implantations mentioned under Section 5.4.2 (thromboangiitis obliterans); a vascular surgeon, an internist and an implanting specialist physician;
- For implantations mentioned under Section 5.4.3 (chronic pancreatitis); a neurosurgeon, an internist and a neuropsychiatrist or psychiatrist;
- For implantations mentioned under Section 5.4.4 (rechargeable SCS); a neurosurgeon, a neurologist or an anaesthetist and a neuropsychiatrist or psychiatrist.

For the latter indication, all members of the multidisciplinary team are required to sign a form prepared by the Insurance Committee, as proposed by the Technical Council for Implants. Furthermore, all documents that prove this indication need to be kept in the patient record, since they can be requested at any time by the advising physician.

5.8.2. Contents of medical report

The medical report required for the request for reimbursement, needs to contain::

- An **anamnesis** mentioning the administered treatments that remained unsuccessful;
- A **diagnosis:**
  - Indicating the nature of the lesions and their irreversible character for implantations mentioned under Section 5.4.1 a) (neurogenic pain syndromes);
  - Indicating thromboangiitis obliterans for implantations mentioned under Section 5.4.2 b);
  - Indicating pain due to chronic pancreatitis for implantations mentioned under Section 5.4.3 c).
- The indication, the **multidisciplinary evaluation** as well as:
  - The psychological and/or psychiatric evaluation, performed prior to the trial for implantations mentioned under Sections 5.4.1 a) and 5.4.3 c) (neurogenic pain syndromes and chronic pancreatitis);
  - The test results including Doppler for implantations mentioned under Section 5.4.2 b) (thromboangiitis obliterans);
- The **results of the trial** as detailed in this report.

5.9. Medical acts relevant to this HTA

The nomenclature of the medical acts relevant to this HTA can be found in following tables. The information in these tables reflects the situation during the second half of 2011, the period the data were assembled.

Table 58 – Neurosurgical acts (Article 14b of R.D. 24.08.1994) concerned by this HTA and related to SCS

nomenclature number		*start date*	label
ambulatory	**hospitalised**		
232492	232503	01.11.1998	Installation of a definitive electrode in intradural position at the occasion of a **test trial**
232853	232864	01.08.1988	Installation of a definitive neurostimulator with the **surgical placement** of the electrode in intradural position
232875	232886	01.08.1988	**Replacement** of a definitive neurostimulator for medullar stimulation
232890	232901	01.08.1988	Placement of a definitive neurostimulator with the **percutaneous placement** of the electrode for the purpose of stimulating the spinal cord, including functional measurements

5

Table 59 – Acts that require the qualification of a specialist physician (Article 11 §1 of R.D. 24.08.1994) concerned by this HTA and related to IADP

nomenclature number		start date	case selection	label
ambulatory	**hospitalised**			
354056	354060	01.07.1986	no	**Implantation** of a subcutaneous drug reservoir connected to a catheter for drug delivery
354292	354303	01.02.2009	no	**Filling** of a programmable pump intended for the delivery of drugs, including cost of materials and/or pump titration with objective evaluation measurement, chargeable maximum six times per year

Nomenclature numbers beyond our data acquisition time-horizon are greyed.

Table 60 – Honoraria of the physician-specialists in anaesthesia (Article 12 §1 of R.D. 24.08.1994) concerned by this HTA and related to IADP

nomenclature number		start date	case selection	label
ambulatory	**hospitalised**			
202716	202720	01.07.2007	no	Placing, subcutaneous tunnelling and fixation of an epidural, intrathecal or plexus catheter for the purpose of long-term infusion of analgesics, with or without image amplification

Table 61 – Neurosurgical acts (Article 14b of R.D. 24.08.1994) concerned by this HTA and related to SCS

nomenclature number		start date	case selection	label	key (2011.08.01)	coefficient
ambulatory	hospitalised					
232492	232503	01.11.1998	no	Installation of a definitive electrode in intradural position at the occasion of a **test trial**	K = 1.319389	75
232853	232864	01.08.1988	no	Installation of a definitive neurostimulator with the **surgical placement** of the electrode in intradural position	K = 1.593161	150
232875	232886	01.08.1988	no	**Replacement** of a definitive neurostimulator for medullar stimulation	K = 1.593161	120
232890	232901	01.08.1988	no	Placement of a definitive neurostimulator with the **percutaneous placement** of the electrode for the purpose of stimulating the spinal cord, including functional measurements	K = 1.593161	80

5.10. Multidisciplinary teams for pain management

The Royal Decree of 13 June 2010, Article 35, §7, 3°) requires the request for reimbursement to be accompanied by a comprehensive medical report drafted and signed by all members of the multidisciplinary team responsible for the implantation and the treatment.

5.11. Belgian referral centres for chronic pain

A detailed description of the Belgian legislation concerning referral centres for chronic pain is beyond the scope of this text. A summary of the working principles and agreement with the registered referral centres can be found below. More detailed information can be obtained from the links on the INAMI–RIZIV web site.[a]

Belgian referral centres for chronic pain are expected to function as a third tier care centre for patients who fulfil the following conditions:

- Who are already receiving chronic pain treatment for at least six months;
- Who moreover were being treated by a specialist physician, and
- Who were referred to the referral centre by their general practitioner or treating specialist physician.

For these patients, a referral centre attempts to establish a multidisciplinary diagnosis, thereby creating the basis for an adequate treatment. When indicated, referral centres may also treat patients with interventional pain management techniques and/or a multidisciplinary revalidation program (i.e. not subject to the agreement about referral centres for chronic pain).

The interventions of the referral centre should be as limited as possible. At the end of a treatment at the referral centre, patients should be referred back to primary or secondary care with recommendations for further treatment.

The referral centres for chronic pain should offer their services to both ambulatory and hospitalised patients.

After receiving a specialised multidisciplinary diagnosis or a multidisciplinary revalidation program, patients are excluded for a period of two years from receiving any other multidisciplinary diagnosis or revalidation program in the same or any other referral centre for chronic pain. However, treatments not subject to the agreement about referral centres for chronic pain are still allowed (e.g. nomenclature acts).

Currently, there are nine registered Belgian referral centres for chronic pain. Those should not to be confounded with the referral centres for chronic fatigue syndrome.

1. U.Z. Antwerpen
2. Hôpital Erasme, Brussels
3. CU Saint-Luc, Brussels
4. CHU de Liège
5. Ziekenhuis Oost-Limburg, Genk
6. CU UCL de Mont-Godinne
7. U.Z. Gent
8. UZ Leuven
9. H.-Hartziekenhuis, Roeselare – Menen

[a] http://www.riziv.be/care/nl/revalidatie/convention/pain/index.htm

6. APPENDIX TO CHAPTER ON REGULATIONS FOR REIMBURSEMENT IN NEIGHBOURING COUNTRIES

6.1. France

Table 62 – Non-rechargeable SCS in France

LPP code	Translated label	implantation	2011 price
3436749	Spinal cord neurostimulator (full system + accessories) MEDTRONIC, ITREL 3	primo	€ 5 685.00
3480294	Spinal cord neurostimulator (replacement) MEDTRONIC, ITREL 3	replacement	€ 5 385.00
3454457	Spinal cord neurostimulator (full system + accessories) MEDTRONIC, PRIMEADVANCED	primo	€ 10 430.00
3495462	Spinal cord neurostimulator (replacement) MEDTRONIC, PRIMEADVANCED	replacement	€ 9 552.00
3477300	Spinal cord neurostimulator (full system + accessories) ST JUDE, GENESIS	primo	€ 5 685.00
3472320	Spinal cord neurostimulator (replacement) ST JUDE, GENESIS	replacement	€ 5 385.00

Table 63 – Rechargeable SCS in France

LPP code	Translated label	implantation	2011 price
3417077	Spinal cord neurostimulator (full system + accessories) ST JUDE, EON	primo	€ 19 807.50
3406412	Spinal cord neurostimulator (replacement) ST JUDE, EON	replacement	€ 16 203.20
3427851	Spinal cord neurostimulator (full system + accessories) MEDTRONIC, RESTORE	primo	€ 20 850.00
3422084	Spinal cord neurostimulator (replacement) MEDTRONIC, RESTORE	replacement	€ 17 056.00
3451163	Spinal cord neurostimulator (full system + accessories) MEDTRONIC, RESTORESENSOR	primo	€ 20 850.00
3498182	Spinal cord neurostimulator (replacement) MEDTRONIC, RESTORESENSOR	replacement	€ 17 056.00
3453417	Spinal cord neurostimulator (full system + accessories) MEDTRONIC, RESTOREULTRA	primo	€ 20 850.00
3426981	Spinal cord neurostimulator (replacement) MEDTRONIC, RESTOREULTRA	replacement	€ 17 056.00
3455215	Spinal cord neurostimulator (full system + accessories) MEDTRONIC, RESTOREADVANCED	primo	€ 20 850.00
3474804	Spinal cord neurostimulator (replacement) MEDTRONIC, RESTOREADVANCED	replacement	€ 17 056.00
3476559	Spinal cord neurostimulator (full system + accessories) BOSTON, PRECISION	primo	€ 19 807.50

3494400	Spinal cord neurostimulator (replacement) BOSTON, PRECISION	replacement	€ 16 203.20

Table 64 – SCS electrodes in France

LPP code	Translated label	2011 price
3420056	4-electrode for SCS neuromodulator MEDTRONIC	€ 650.00
3433834	4-electrode for SCS neuromodulator ST JUDE, GENESIS	€ 650.00
3466532	8-electrode for SCS neuromodulator BOSTON, LINEAR	€ 650.00
3482229	8-electrode for SCS neuromodulator MEDTRONIC,OCTAD or SPECIFY	€ 650.00
3487557	16-electrode for SCS neuromodulator BOSTON, ARTISAN	€ 650.00
3492044	8-electrode for SCS neuromodulator MEDTRONIC,OCTAD or SPECIFY	€ 650.00

Table 65 – IADP in France

LPP code	Translated label	2011 price
3402466	Programmable implantable pump with variable pump (for administration of baclofene or analgesics) MEDTRONIC, Synchromed II	€ 6186.00

Non programmable IADP and programmable IADP with continuous pump are not anymore included in the LPP since 2010.

6.2. The Netherlands

Table 66 – DBC code for SCS and IADP (2011)[190] in the Netherlands

DBC code	Description	Hopital costs	Physician fees	Total (2011)
08110027050038	Regular care / spine: placement or revision of stimulator or pump / Epidural spinal cord stimulation	€ 22 745.63	€ 1 029.92	€ 23 775.55

6.3. Germany

Table 67 – Supplemental fees for SCS in addition to DRG funding (2011)[138] in Germany

ZE code	Description	OPS code	OPS description	ZE amount*
ZE87	Single-channel non-rechargeable neurostimulator for spinal cord stimulation (SCS) or Peripheral nerve stimulation (PNS) stimulation	5-039.e0	Implantation or replacement of a non-rechargeable SCS with implantation or replacement of a single electrode	€ 6 931.88
		5-039.f0	Replacement of a non-rechargeable SCS without replacement of an electrode	
ZE127	Multi-channel, non-rechargeable neurostimulator for SCS or PNS stimulation	5-039.e1	Implantation or replacement of a non-rechargeable, multichannel SCS with implantation or replacement of the electrode	€ 11 839.98
		5-039.f1	Replacement of a non-rechargeable, multichannel SCS without replacement of the electrode	
ZE2011-61**	Multi-channel, rechargeable neurostimulator for DBS, SCS, or stimulation of the peripheral nervous system	5-039.e2	Implantation or replacement of a rechargeable, multichannel SCS with implantation or replacement of the electrode	Range: € 19 000 - € 22 000
		5-039.f2	Replacement of a rechargeable, multichannel SCS without replacement of the electrode	Range: € 17 000 - € 22 000.00

** includes active implant, electrodes, catheter, patient programmer and/or other accessories as well as the honorarium of the hospital physician. ** For these treatments, supplemental fees were to be negotiated on a hospital-by-hospital basis in contract between hospitals and sickness funds in accordance to §6 Section 1, 1) of the Hospital Reimbursement Act (Krankenhausentgeltgesetz, KHEntgG).). Ranges estimated for ZE2011-61 in this table are based on published agreements with three German hospitals (http://www.ukaachen.de/;, http://www.sozialstiftung-bamberg.de/; and http://www.ukb.uni-bonn.de/)*

Table 68 – Supplemental fees for IADP (2011)[138] in Germany

ZE code	Description	OPS code	OPS description	ZE amount*
ZE09	Fully implantable drug pump with programmable variable day profile	5-038.41	Implantation or replacement of a fully implantable drug pump with programmable variable day profile	€ 10 523.09
ZE56	Fully implantable drug pump with constant flow rate	5-038.40	Implantation or replacement of a fully implantable drug pump with constant flow rate	€ 3 966.36
ZE2011-07*	Other implantable drug pumps	5-038.4x	Implantation or replacement of other implantable drug pumps	€ 4 840.30

** For these more advanced treatments, supplementary fees were to be negotiated on a hospital-by-hospital basis in contracts between hospitals and sickness funds in accordance to §6 Section 1, 1) of the Hospital Reimbursement Act (Krankenhausentgeltgesetz, KHEntgG. ZE2011-07 estimate in this table is based on published agreements with one German hospital (http://www.ukaachen.de/).*

6.4. UK

Table 69 – HRG and procedure codes related to SCS indicating specialised pain management services (2011)[146, 147] in the UK

Procedure codes (OPCS 4.6)	HRG4 related Codes	HRG 2011-2012 Tariffs Combined day case / elective tariff	HRG 2011-2012 Tariffs Non elective spell tariff
A48.3 Insertion of neurostimulator adjacent to spinal cord	AB01Z Complex Neurosurgical Pain Procedures	£2503	£5574
A48.4 Attention to neurostimulator adjacent to spinal cord NEC	AB05 Intermediate Pain Procedures	£518	£2400

Table 70 – HRG and procedure codes related to IADP indicating specialised pain management services (2011)[146, 147] in the UK

Procedure codes (OPCS 4.6)	HRG4 related Codes	HRG 2011-2012 Tariffs Combined day case / elective tariff	HRG 2011-2012 Tariffs Non elective spell tariff
A54.3 Implantation of intrathecal drug delivery device adjacent to spinal cord	AB01Z Complex Neurosurgical Pain Procedures	£2503	£5574
A54.4 Attention to intrathecal drug delivery device adjacent to spinal cord	AB05 Intermediate Pain Procedures	£518	£2400
A54.5 Removal of intrathecal drug delivery device adjacent to spinal cord	AB02 Complex Major Pain Procedures	£708	£5025

7. APPENDIX TO CHAPTER ON NEUROMODULATION USE IN BELGIUM

7.1. Methodology

Table 71 – Selection pseudo-codes

Pseudo-codes (Ambulatory-Hospitalization)	Dutch label	French label
683093-683104	Ingeplante neurostimulator, inclusief patient programmer	**Neurostimulateur implanté, le programmateur patient inclus**
688251-688262	Neurostimulator - hernieuwing in geval van end of life	**Neurostimulateur - renouvellement en cas d'end of life**
688273-688284	Neurostimulator - hernieuwing in geval van infectie	**Neurostimulateur - renouvellement en cas d'infection**
683115-683126	Ingeplante elektrode en toebehoren voor neurostimulator	**Electrode implantée et accessoires pour neurostimulateur**
683152-683163	Programmeerbare implanteerbare elektronisch gestuurde pomp met regelbaar debiet bestemd voor intrathecale toediening van morfine of van een morfinomimeticum	**Pompe programmable implantable commandée électroniquement, à débit réglable destinée à l'administration intrathécale de morphine ou d'un agent**
683196-683200	Implanteerbare pomp met constant debiet bestemd voor intrathecale toediening van morfine of van een morfinomimeticum	**Pompe implantable à débit constant destinée à l'administration intrathécale de morphine ou d'un agent morphinomimétique**
683336-683340	Reservoir met epidurale of intrathecale enkele of dubbele catheder voor herhaalde transcutane injecties	**Réservoir avec cathéter épidural ou intrathécal simple ou double pour injections transcutanées répétées**

During the data analyses, rechargeable SCS were identified by the pseudo-code 715116, 715120 (first rechargeable neurostimulator), 715131 or 715142 (replacement rechargeable neurostimulator).

7.2. Descriptive analyses

7.2.1. Baseline data

Selecting only the stays during which a neurostimulator or/and an IAD pump was recorded, we found 5485 stays during which the relevant pseudo-codes were registered between 2002 and 2009 corresponding to 4792 classic hospitalizations and 693 one-day hospitalizations. However, it is important to note that one-day stays were included in the data only from 2006 onwards. Those data are shown in the first part of Table 72.

Table 72 – Selection of stays based on the presence of pseudo-codes related to a neurostimulator and/or an IAD pump (2002-2009)

STEP 1 : INITIAL SELECTION (discharge year)

AZV/ADH-SHA/HJA	2002	2003	2004	2005	2006	2007	2008	2009	TOTAL	
SCS										
Classic hospitalisation	358	353	454	465	420	480	554	500	**3584**	**4259**
Oneday					145	177	161	192	**675**	
IADP										
Classic hospitalisation	139	148	155	127	132	151	161	199	**1212**	**1230**
Oneday					3	2	7	6	**18**	
BOTH										
Classic hospitalisation		1			1		1	1	**4**	
Oneday										
TOTAL										
Classic hospitalisation	**497**	**500**	**609**	**592**	**551**	**631**	**714**	**698**	**4792**	**5485**
Oneday					**148**	**179**	**168**	**198**	**693**	

STEP 2 : COUPLED STAYS (discharge year)

AZV/ADH-SHA/HJA + MKG/RCM	2002	2003	2004	2005	2006	2007	2008	2009	TOTAL	
SCS										
Classic hospitalisation	335	334	427	456	415	474	546		**2987**	**3443**
Oneday					125	174	157		**456**	
IADP										
Classic hospitalisation	130	138	143	122	130	149	158		**970**	**981**
Oneday					2	2	7		**11**	
BOTH										
Classic hospitalisation		1			1		1		**3**	
Oneday										
TOTAL										
Classic hospitalisation	**465**	**471**	**570**	**578**	**544**	**623**	**703**		**3954**	**4421**
Oneday					**127**	**176**	**164**		**467**	

In a second step, we only kept the coupled stays, which means that we kept the stays for which also the clinical data were available. For 2009 stays this was not possible since 2009 clinical data were not coupled yet at the moment of data analysis. Therefore, the nomenclature data of those 2009 stays will be analysed separately.

Table 73 – Selection of implants based on the presence of pseudo-codes related to a neurostimulator and/or a IAD pump (2002-2008)

STEP 3 : IMPLANTATION (implantation year)

AZV/ADH-SHA/HJA + MKG/RCM	2001	2002	2003	2004	2005	2006	2007	2008	2009	TOTAL	
SCS											
Classic hospitalisation	1	335	333	427	458	414	475	545		**2988**	**3444**
Oneday						125	174	157		**456**	
IADP											
Classic hospitalisation	1	95	115	105	88	92	101	116		**713**	**718**
Oneday							2	3		**5**	
BOTH											
Classic hospitalisation			1			1		1		**3**	
Oneday											
TOTAL											
Classic hospitalisation	**2**	**430**	**447**	**532**	**546**	**505**	**576**	**660**		**3698**	**4159**
Oneday						**125**	**176**	**160**		**461**	

Each row gives unique stays or unique events, the total may be inferior to the added rows .

Finally, the third step consisted in isolating the implants and the date they were done as distinct events. Table 73 shows that there were 3444 neurostimulators implanted during 3443 (classic) stays, because 2 devices were implanted within an interval of 2 months during the same stay. Two other implants were performed in 2001 during two stays with discharge date in 2002 (record year). A total of 14 SCS implants were done in one-day hospitalization with a reimbursement of € 0 (this may be devices that are offered by the manufacturer during a warranty period). The same occurred for one IADP implantation. The number of devices registered per implantation was 1 in 98.69% of the SCS cases and in 59.8% of the IADP implants only (2 devices were recorded in 38% of the IADP implants, including an accessory like the catheter). However, we assumed that only one implant was implanted on a single day.

Based on the amounts reimbursed under an IADP pseudo-code, we discovered several amounts recorded with a IAD pump pseudo-code but obviously related to a catheter or a Personal Therapy Manager. Therefore, we discarded any IADP implantation for an amount equals or less than € 1000, which left 718 implants (implanted during 718 stays).

In total, there were 3 stays during which a SCS and an IADP implantations were both performed. Without counting them twice, there were 4159 selected stays, for a total of 4162 implants between 2002 and 2008.

In 2009, there were 693 SCS implants and 156 IAD pumps implants in our data. One neurostimulator was implanted during the same stay as a IADP pump (not on the same date). And two other SCS implants occurred at 13 months apart during the same (very long) stay.

During the analysis we became aware of a missing nomenclature couple 686232-686243. Verification in the N-documents learned that this concerned only 9 occurences in the period 2002-2008.

7.2.2. Under- and over-reporting in the data

There are some discrepancies in the numbers of neurostimulators or IADP present in the aggregated N Documents dataset of the RIZIV–INAMI and in the Hospital and Day Care Billing Data (AZV/ADH–SHA/HJA) of the same institution.

Table 74 presents the number of cases for 2006 and 2007 (for which all bills have now been processed) for the code 683104 Neurostimulator, including patient programmer (implanted in classic hospitalization). The reported numbers are 18% lower in the AZV/ADH–SHA/HJA data. The main raison being a late billing of the procedures in some cases of implants billing. As for all procedures (acts), implants may be billed until 18 months after the implantation. As seen for the code 683104 in Table 75, in some cases of implants are still (abnormally) processed 2 or 3 years after implantation. Late regularisations are then introduced in the N documents but not in the AZV/ADH–SHA/HJA, which is closed yet. The same phenomenon was even more pronounced in one-day (code 683093), where the numbers were 38 % lower than the numbers reported in the N documents for the same period (2006-2007) and 27% lower in 2009.

Table 74 – Code 683104: Number of cases recorded per year in N documents and AZV/ADH–SHA/HJA (2006-2007)

	2006	2007	Total
N documents	497	616	1113
AZV/ADH-SHA/HJA	423	495	918
	85.1%	80.4%	82%

Source: RIZIV–INAMI

Table 75 – Code 683104: Number of cases recorded per year in N documents (billing 2006-2010)

Number of cases	Billing year					
Implantation year	2006	2007	2008	2009	2010	Grand Total
2003	18					18
2004	29	30				59
2005	202	40	21			263
2006	248	201	25	23		497
2007		305	222	38	51	616
2008			352	254	32	638
2009				322	217	539
2010					216	216
Grand Total	497	576	620	637	516	2846

Source: RIZIV–INAMI – 2010 results only cover the 5 first months of the year.

Table 76 – Number of implants estimated per year

Device	2002	2003	2004	2005	2006	2007	2008	2009	2010 (partial)
Neurostimulators	654	688	740	761	759	846	919	889	553
Rechargeable neurostimulators								21	143
IADP	147	187	159	115	128	131	156	197	95

Source: based on N documents and Clinical and Billing data

7.2.3. Patient characteristics

Table 77 – Age and gender distribution for the 3444 SCS implants and 718 IADP implants (2002-2008)

Age at implantation date	SCS			IADP		
	Male	Female	Total	Male	Female	Total
Before 30 years	9	30	39 (1.13%)	5	8	13 (1.81%)
30 to 39 years	148	247	395 (11.47%)	17	21	38 (5.29%)
40 to 49 years	425	675	1100 (31.94%)	92	114	206 (28.69%)
50 to 59 years	451	650	1101 (31.97%)	102	131	233 (32.45%)
60 to 69 years	189	315	504 (14.63%)	52	78	130 (18.11%)
70 to 79 years	97	179	276 (8.01%)	30	46	76 (10.58%)
80 to 89 years	13	16	29 (0.84%)	3	17	20 (2.79%)
90 to 99 years	0	0	0	0	2	2 (0.28%)
TOTAL	1332 (38.68%)	2112 (61.32%)	3444 (100%)	301 (41.92%)	417 (58.08%)	718 (100%)

Table 78 – Age distribution parameters for the 3444 SCS implants and 718 IADP implants (2002-2008)

Analysis Variable : Age at implantation date								
Type implantation	Nb implantations	Mean	Std Dev	Min.	25th Pctl	Median	75th Pctl	Max.
SCS	3444	51.9	11.4	13.0	44.0	51.0	59.0	86.0
IADP	718	54.8	12.1	6.0	47.0	53.0	62.0	93.0

7.2.4. Hospitalization Diagnoses

Table 79 – Top 20 Principal diagnosis in 3 digits for the 3444 SCS implants (2002-2008)

Principal diagnosis in 3 digits: SCS		N	%	Cumulative frequency	Cumul %
V53	Fitting and adjustment of other device	1135	32.96	1135	32.96
722	Intervertebral disc disorders	656	19.05	1791	52.00
724	Other and unspecified disorders of back	487	14.14	2278	66.14
996	Complications peculiar to certain specified procedures	339	9.84	2617	75.99
355	Mononeuritis of lower limb	183	5.31	2800	81.30
353	Nerve root and plexus disorders	102	2.96	2902	84.26
723	Other disorders of cervical region	77	2.24	2979	86.50
729	Other disorders of soft tissues	63	1.83	3042	88.33
998	Other complications of procedures, NEC	58	1.68	3100	90.01
721	Spondylosis and allied disorders	50	1.45	3150	91.46
V72	Special investigations and examinations	38	1.10	3188	92.57
733	Other disorders of bone and cartilage	37	1.07	3225	93.64
356	Hereditary and idiopathic peripheral neuropathy	30	0.87	3255	94.51
354	Mononeuritis of upper limb and mononeuritis multiplex	28	0.81	3283	95.33
350	Trigeminal nerve disorders	17	0.49	3300	95.82
357	Inflammatory and toxic neuropathy	12	0.35	3312	96.17
440	Atherosclerosis	11	0.32	3323	96.49
346	Migraine	10	0.29	3333	96.78
332	Parkinson's disease	8	0.23	3341	97.01
250	Diabetes mellitus	7	0.20	3348	97.21
Other diagnoses		96	0.03	3444	100.00

Table 80 – Top 20 Principal diagnosis in 3 digits for the 718 implants IADP (2002-2008)

Principal diagnosis in 3 digits: IADP		N	%	Cumulative frequency	Cumul %
V53	Fitting and adjustment of other device	162	22.56	162	22.56
722	Intervertebral disc disorders	159	22.14	321	44.71
724	Other and unspecified disorders of back	128	17.83	449	62.53
996	Complications peculiar to certain specified procedures	127	17.69	576	80.22
721	Spondylosis and allied disorders	21	2.92	597	83.15
998	Other complications of procedures, NEC	17	2.37	614	85.52
355	Mononeuritis of lower limb	11	1.53	625	87.05
344	Other paralytic syndromes	8	1.11	633	88.16
723	Other disorders of cervical region	7	0.97	640	89.14
V58	Encounter for other and unspecified procedures and aftercare	6	0.84	646	89.97
353	Nerve root and plexus disorders	5	0.70	651	90.67
340	Multiple sclerosis	4	0.56	655	91.23
349	Other and unspecified disorders of the nervous system	4	0.56	659	91.78
729	Other disorders of soft tissues	4	0.56	663	92.34
733	Other disorders of bone and cartilage	4	0.56	667	92.90
780	General symptoms	4	0.56	671	93.45
336	Other diseases of spinal cord	3	0.42	674	93.87
343	Infantile cerebral palsy	3	0.42	677	94.29
356	Hereditary and idiopathic peripheral neuropathy	3	0.42	680	94.71
719	Other and unspecified disorders of joint	3	0.42	683	95.13
Other diagnoses		35	0.05	718	100.00

Disregarding the “aspecific” codes beginning by a “V” (factors influencing health status and contact with health services), “D” (psychiatric stays), “U” (admissions in emergency), “M” (certain one-day stays) or between “996-999” (complications of care), the diagnosis 722.83 ‘Postlaminectomy syndrome, lumbar region’ was encoded as principal diagnosis in 17.5 % of the SCS implants and 19.1% of the IADP implants (Table 81 et Table 82) .

Table 81 – Top 20 SPECIFIC Principal diagnosis in 5 digits for the 1865 SCS implants (aspecific principal diagnoses excluded) (2002-2008)

Principal diagnosis in 5 digits: SCS	N	%	Cumulative frequency	Cumul %
72283 Postlaminectomy syndrome, lumbar region	**327**	**17.53**	**327**	**17.53**
7243 Sciatia	**171**	**9.17**	**498**	**26.70**
7242 Lumbago	**137**	**7.35**	**635**	**34.05**
72280 Postlaminectomy syndrome, unspecified region	**108**	**5.79**	**743**	**39.84**
3558 Mononeuritis of lower limb, unspecified	**99**	**5.31**	**842**	**45.15**
7244 Thoracic or lumbosacral neuritis or radiculitis, unspecified	77	4.13	919	49.28
72210 Lumbar intervertebral disc without myelopathy	73	3.91	992	53.19
7245 Backache, unspecified	59	3.16	1051	56.35
72282 Postlaminectomy syndrome, thoracic region	58	3.11	1109	59.46
35579 Other mononeuritis of lower limb	56	3.00	1165	62.47
3534 Lumbosacral root lesions, not elsewhere classified	46	2.47	1211	64.93
72252 Lumbar or lumbosacral intervertebral disc	44	2.36	1255	67.29
7337 Algoneurodystrophy	35	1.88	1290	69.17
7292 Neuralgia, neuritis, and radiculitis, unspecified	33	1.77	1323	70.94
7213 Lumbosacral spondylosis without myelopathy	29	1.55	1352	72.49
7233 Cervicobrachial syndrome (diffuse)	29	1.55	1381	74.05
7295 Pain in limb	23	1.23	1404	75.28
7231 Cervicalgia	20	1.07	1424	76.35
72402 Spinal stenosis,lumbar region	19	1.02	1443	77.37
7234 Brachia neuritis or radiculitis NOS	17	0.91	1460	78.28
Others	405	21.72	1865	100.0

Table 82 – Top 20 SPECIFIC Principal diagnosis in 5 digits for the 403 implants IADP (aspecific principal diagnoses excluded) (2002-2008)

Principal diagnosis in 5 digits: IADP	N	%	Cumulative frequency	Cumul %
72283 Postlaminectomy syndrome, lumbar region	**77**	**19.11**	**77**	**19.11**
7242 Lumbago	**67**	**16.63**	**144**	**35.73**
72280 Postlaminectomy syndrome, unspecified region	**38**	**9.43**	**182**	**45.16**
7245 Backache, unspecified	**24**	**5.96**	**206**	**51.12**
7243 Sciatia	**17**	**4.22**	**223**	**55.33**
72210 Lumbar intervertebral disc without myelopathy	15	3.72	238	59.06
7213 Lumbosacral spondylosis without myelopathy	12	2.98	250	62.03
72252 Lumbar or lumbosacral intervertebral disc	10	2.48	260	64.52
72282 Postlaminectomy syndrome, thoracic region	7	1.74	267	66.25
7244 Thoracic or lumbosacral neuritis or radiculitis, unspecified	7	1.74	274	67.99
72402 Spinal stenosis,lumbar region	6	1.49	280	69.48
7246 Disorders of sacrum	6	1.49	286	70.97
72142 Lumbar region	5	1.24	291	72.21
340 Multiple sclerosis	4	0.99	295	73.20
3558 Mononeuritis of lower limb, unspecified	4	0.99	299	74.19
34400 Quadriplegia, unspecified	3	0.74	302	74.94
3449 Paralysis, unspecified	3	0.74	305	75.68
3538 Other nerve root and plexus disorders	3	0.74	308	76.43
3559 Mononeuritis of unspecified site	3	0.74	311	77.17
72190 Spondylosis of unspecified site without mention of myelopathy	3	0.74	314	77.92
Others	89	22.08	403	100.0

Table 83 and Table 84 present the secondary diagnoses that were encoded for the 1865 SCS implants and 403 implants with a “specific” principal diagnosis. Again, secondary diagnosis codes not speaking for themselves were not included.

Table 83 – Top 20 SPECIFIC secondary diagnoses in 5 digits for 1865 SCS implants and 403 implants IADP (2002-2008)

Secondary diagnoses in 5 digits: SCS	Freq	%
ABSENCE of secondary diagnosis	501	26.9%
3051 Tobacco use disorder	159	8.5%
4011 Essential hypertension benign	115	6.2%
72283 Postlaminectomy syndrome, lumbar region	106	5.7%
7213 Lumbosacral spondylosis without myelopathy	98	5.3%
7243 Sciatia	74	4.0%
4019 Essential hypertension unspecified	71	3.8%
7242 Lumbago	71	3.8%
25000 Diabetes mellitus without mention of complication, type II or unsp	70	3.8%
2720 Pure hypercholesterolemia	68	3.6%
27800 Obesity, unspecified	65	3.5%
72252 Lumbar or lumbosacral intervertebral disc	48	2.6%
49120 Obstructive chronic bronchitis without exacerbation	39	2.1%
311 Depressive disorder, not elsewhere classified	36	1.9%
7840 Headache	30	1.6%
72210 Lumbar intervertebral disc without myelopathy	25	1.3%
7820 Disturbance of skin sensation	22	1.2%
7337 Algoneurodystrophy	21	1.1%
412 Old myocardial infarction	20	1.1%
7245 Backache, unspecified	19	1.0%

Table 84 – Top 20 SPECIFIC secondary diagnoses in 5 digits for 1865 SCS implants and 403 implants IADP (2002-2008)

Secondary diagnoses in 5 digits: IADP	Freq	%
ABSENCE of secondary diagnosis	131	7.0%
72283 Postlaminectomy syndrome, lumbar region	55	2.9%
4011 Essential hypertension benign	42	2.3%
7243 Sciatia	42	2.3%
3051 Tobacco use disorder	41	2.2%
72280 Postlaminectomy syndrome, unspecified region	36	1.9%
7242 Lumbago	33	1.8%
4019 Essential hypertension unspecified	30	1.6%
27800 Obesity, unspecified	29	1.6%
25000 Diabetes mellitus without mention of complication, type II or unsp	26	1.4%
49120 Obstructive chronic bronchitis without exacerbation	26	1.4%
2720 Pure hypercholesterolemia	23	1.2%
7213 Lumbosacral spondylosis without myelopathy	20	1.1%
73300 Osteoporosis, unspecified	17	0.9%
72252 Lumbar or lumbosacral intervertebral disc	16	0.9%
311 Depressive disorder, not elsewhere classified	15	0.8%
7245 Backache, unspecified	15	0.8%
E8497 Place of occurrence, Residential institution	14	0.8%
3441 Paraplegia	13	0.7%
7291 Myalgia and myositis, unspecified	13	0.7%

The secondary diagnoses presented in Table 85 and Table 86 are related to the implants with an inaccurate principal diagnosis (such as V53, 996 etc.).

Table 85 – Top 20 SPECIFIC secondary diagnoses in 5 digits for the 1579 SCS implants and 315 implants IADP with an ASPECIFIC Principal diagnosis (2002-2008)

Secondary diagnoses in 5 digits: SCS	Freq	%
ABSENCE of secondary diagnosis	418	26.5%
72280 Postlaminectomy syndrome, unspecified region	249	15.8%
72283 Postlaminectomy syndrome, lumbar region	175	11.1%
7243 Sciatia	99	6.3%
3051 Tobacco use disorder	90	5.7%
7242 Lumbago	90	5.7%
4011 Essential hypertension benign	58	3.7%
25000 Diabetes mellitus without mention of complication, type II or unsp	46	2.9%
7337 Algoneurodystrophy	39	2.5%
27800 Obesity, unspecified	38	2.4%
7213 Lumbosacral spondylosis without myelopathy	37	2.3%
2720 Pure hypercholesterolemia	34	2.2%
4019 Essential hypertension unspecified	33	2.1%
72252 Lumbar or lumbosacral intervertebral disc	31	2.0%
49120 Obstructive chronic bronchitis without exacerbation	29	1.8%
311 Depressive disorder, not elsewhere classified	28	1.8%
7233 Cervicobrachial syndrome (diffuse)	21	1.3%
E8781 Surgical operation with implant of artificial internal device	21	1.3%
3558 Mononeuritis of lower limb, unspecified	16	1.0%
7244 Thoracic or lumbosacral neuritis or radiculitis, unspecified	16	1.0%

Table 86 – Top 20 SPECIFIC secondary diagnoses in 5 digits for the 1579 SCS implants and 315 implants IADP with an ASPECIFIC Principal diagnosis (2002-2008)

Secondary diagnoses in 5 digits: IADP	Freq	%
ABSENCE of secondary diagnosis	58	18.4%
72283 Postlaminectomy syndrome, lumbar region	39	12.4%
72280 Postlaminectomy syndrome, unspecified region	33	10.5%
4011 Essential hypertension benign	20	6.3%
7242 Lumbago	17	5.4%
7243 Sciatia	16	5.1%
3051 Tobacco use disorder	14	4.4%
25000 Diabetes mellitus without mention of complication, type II or unsp	13	4.1%
49120 Obstructive chronic bronchitis without exacerbation	13	4.1%
3441 Paraplegia	10	3.2%
5771 Chronic pancreatitis	10	3.2%
7213 Lumbosacral spondylosis without myelopathy	10	3.2%
E8497 Place of occurrence, Residential institution	10	3.2%
E8781 Surgical operation with implant of artificial internal device	10	3.2%
73300 Osteoporosis, unspecified	8	2.5%
2720 Pure hypercholesterolemia	7	2.2%
2920 Drug withdrawal	7	2.2%
4019 Essential hypertension unspecified	7	2.2%
E8798 Other specified procedures	7	2.2%
27800 Obesity, unspecified	6	1.9%

7.2.5. Implants Geography

Table 87 – SCS Patient residence and hospital localisation (2002-2008)

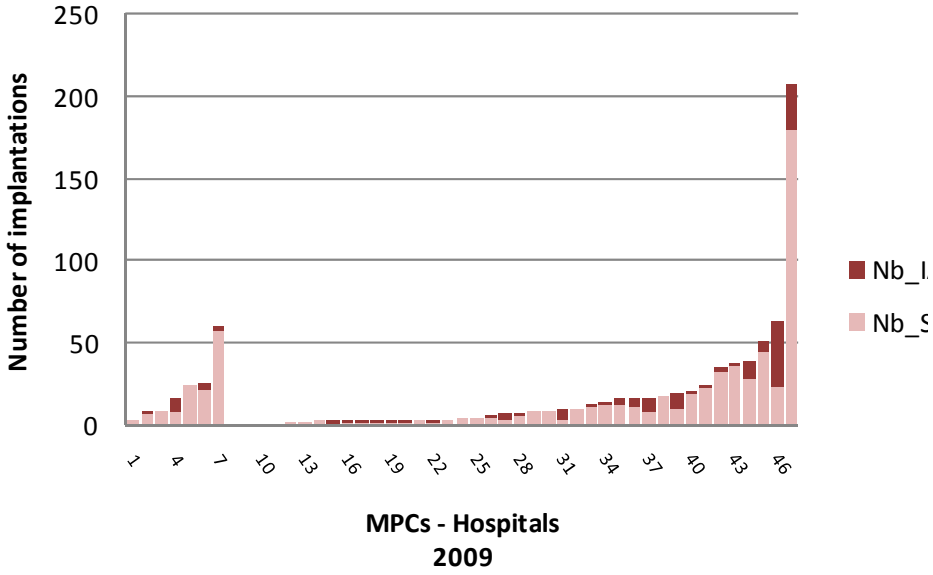
HOSPITAL? PATIENT ?	Antwerpen	Brabant wallon	Bruxelles-Capitale	Hainaut	Limburg	Liège	Luxembourg	Namur	Oost-Vlaanderen	Vlaams Brabant	West-Vlaanderen	Total
0000	0	0	0	1	1	0	0	0	13	2	15	**32 0.9%**
Antwerpen	286	0	0	0	21	0	0	0	336	26	4	**673 19.5%**
Brabant wallon	0	36	10	2	1	0	0	12	0	0	0	**61 1.7%**
Bruxelles-Capitale	0	3	49	0	1	0	0	2	8	2	1	**66 1.9%**
Hainaut	0	7	33	80	0	3	0	13	10	2	13	**161 4.7%**
Limburg	6	0	1	0	276	5	0	0	32	27	0	**347 10.1%**
Liège	0	1	4	0	1	280	0	2	0	0	0	**288 8.4%**
Luxembourg	0	15	3	0	0	7	3	1	0	0	0	**29 0.8%**
Namur	0	5	6	5	0	6	0	64	0	1	1	**88 2.6%**
Oost-Vlaanderen	16	0	5	1	0	0	0	0	876	10	29	**937 27.2%**
Vlaams Brabant	27	4	16	0	27	1	0	1	91	41	5	**213 6.2%**
West-Vlaanderen	4	0	1	1	1	0	0	0	125	6	411	**549 15.9%**
Total	**339 9.8%**	**71 2.1%**	**128 3.7%**	**90 2.6%**	**329 9.6%**	**302 8.8%**	**3 0.1%**	**95 2.8%**	**1491 43.3%**	**117 3.4%0**	**479 13.9%1**	**3444 100%**

Table 88 – IADP Patient residence and hospital localisation (2002-2008)

HOSPITAL? PATIENT ?	Antwerpen	Brabant wallon	Bruxelles-Capitale	Hainaut	Limburg	Liège	Luxembourg	Namur	Oost-Vlaanderen	Vlaams Brabant	West-Vlaanderen	Total
0000	0	0	0	0	1	0	0	0	1	0	8	**10 1.4%**
Antwerpen	78	0	1	0	2	0	0	0	57	6	2	**146 20.3%**
Brabant wallon	0	5	1	0	0	0	0	0	0	0	0	**6 0.8%**
Bruxelles-Capitale	0	1	3	0	0	0	0	0	0	0	2	**6 0.8%**
Hainaut	0	0	3	3	0	0	0	0	1	0	3	**10 1.4%**
Limburg	2	0	0	0	34	0	0	0	3	3	5	**47 6.6%**
Liège	0	1	1	0	0	33	0	0	2	0	2	**39 5.4%**
Luxembourg	0	2	0	0	0	1	0	1	0	0	0	**4 0.6%**
Namur	0	1	3	0	0	0	0	8	0	0	0	**12 1.7%**
Oost-Vlaanderen	2	0	0	0	0	0	0	0	185	0	11	**198 27.6%**
Vlaams Brabant	4	0	4	0	0	0	0	0	18	1	4	**31 4.3%**
West-Vlaanderen	1	0	0	0	0	0	0	0	30	0	178	**209 29.1%**
Total	**87 12.1%**	**10 1.4%**	**16 2.2%**	**3 0.4%**	**37 5.2%**	**34 4.7%**	**0 0%**	**9 1.3%**	**297 41.4%**	**10 1.4%**	**215 29.9%**	**718 100%**

7.2.6. Number of implants per hospital

Figure 17 – Number of SCS or IADP implants per hospital (2009)



7.2.7. Patient chronology

Table 89 – Number of implants per patient : SCS or IADP implants (2002-2008)

Number of implants per patient	Frequency	Percent	Cumulative Frequency	Cumulative Percentage
1	2954	85.20	2954	85.20
2	385	11.10	3339	96.31
3	96	2.77	3435	99.08
4	18	0.52	3453	99.60
5	10	0.29	3463	99.88
6	2	0.06	3465	99.94
7	1	0.03	3466	99.97
9	1	0.03	3467	100.00

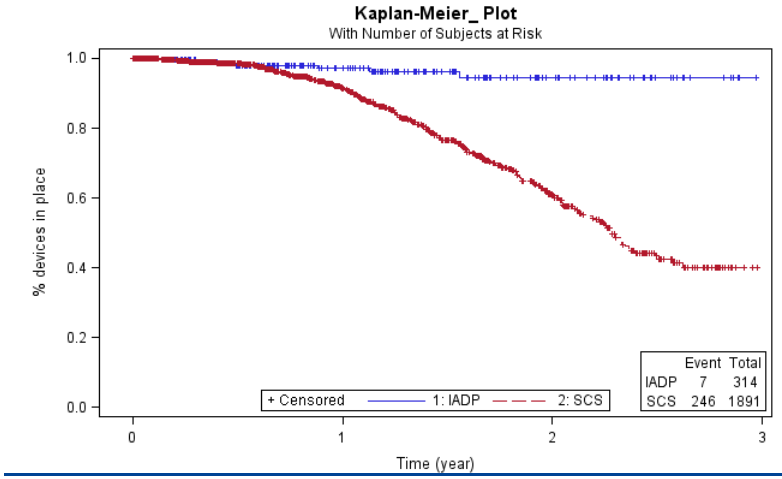
Table 90 – Detailed patient's chronology of SCS or IADP implants between 2002 and 2008 (2002-2008)

SCS or IADP implantation sequence per patient	Frequency	Percent
IADP	614	17.7%
IADP_IADP	19	0.5%
IADP_IADP_IADP	1	0.0%
SCS	2340	67.5%
SCS _SCS	329	9.5%
SCS _SCS _SCS or more SCS implantations	103	3.0%
SCS_IADP (or vice versa)	37	1.1%
Combinations of 3 or more SCS & IADP implantations	24	0.7%

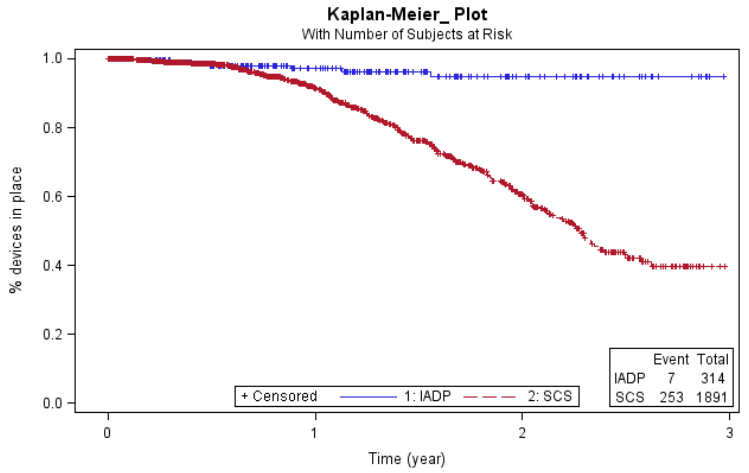
7.3. Device Survival

Figure 18 – Device lifetime after implantation (2006-2008), analyses 5-8

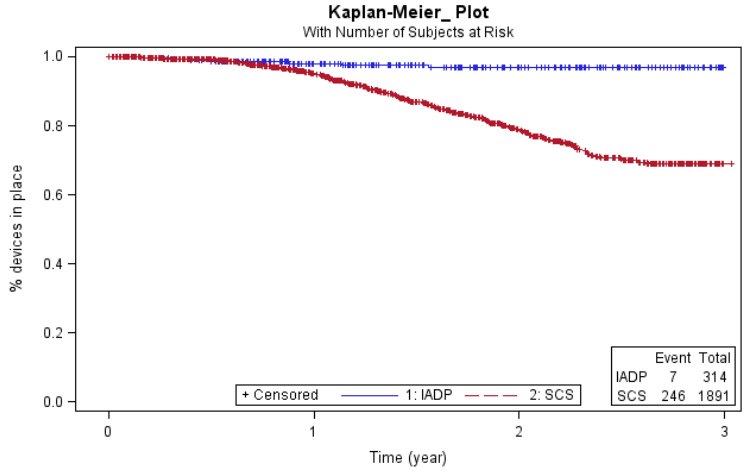
Analysis 5 (SCS median time=2.28 years (CI: 2.14-2.49))



Analysis 6 (SCS median time=2.28 years (CI: 2.12 -2.40))



Analysis 7



Analysis 8

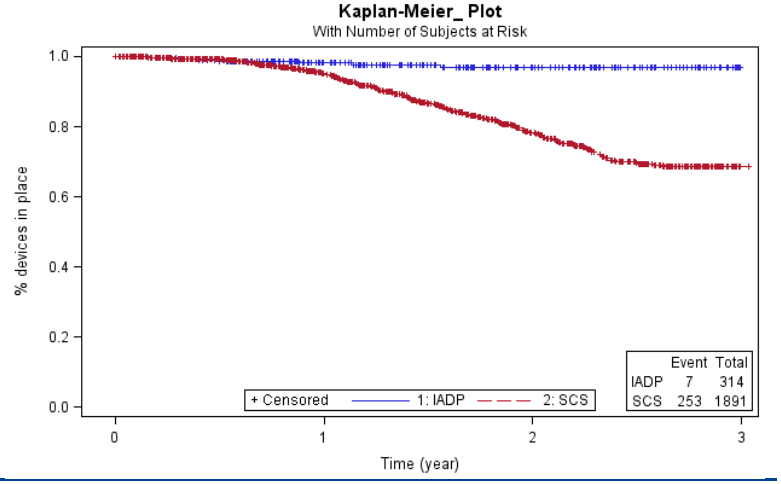


Table 91 – Replacement rate (2006-2008)

Device type	Nb implantations	Replaced	Censored	Percent Censored	Replacement rate at 1 year	at 2 years
SCS	1891	246	1645	86.99	8.69	38.83
IADP	314	7	307	97.77	2.93	5.39
Total	**2205**	**253**	**1952**	**88.53**		

Analysis 6

Device type	Nb implantations	Replaced	Censored	Percent Censored	Replacement rate at 1 year	at 2 years
SCS	1891	253	1638	86.62	8.64	39.81
IADP	314	7	307	97.77	2.84	5.23
Total	**2205**	**260**	**1945**	**88.21**		

Analysis 7

Device type	Nb implantations	Replaced	Censored	Percent Censored	Replacement rate at 1 year	at 2 years
SCS	1891	246	1645	86.99	5.00	21.16
IADP	314	7	307	97.77	1.92	3.28
Total	**2205**	**253**	**1952**	**88.53**		

Analysis 8

Device type	Nb implantations	Replaced	Censored	Percent Censored	Replacement rate at 1 year	at 2 years
SCS	1891	253	1638	86.62	4.98	21.61
IADP	314	7	307	97.77	1.87	3.14
Total	**2205**	**260**	**1945**	**88.21**		

Table 92 – Replacement rate par 100 person-years (2006-2008)

ANALYSIS 5

Time Interval	SCS Number Interval	SCS Number Censored	SCS Number Failed	SCS Person-Years	SCS Event Rate (%)	IADP Number Interval	IADP Number Censored	IADP Number Failed	IADP Person-Years	IADP Event Rate (%)
[0,1)	1891	1212	71	899.36	7.89	314	197	5	168.73	2.96
[1,2)	608	312	138	365.00	37.81	112	75	2	70.19	2.85
[2,3)	158	121	37	57.80	64.01	35	35	0	15.83	0
Overall	**2657**	**1645**	**246**	**1322.17**	**18.61**	**461**	**307**	**7**	**254.75**	**2.75**

ANALYSIS 6

Time Interval	SCS Number Interval	SCS Number Censored	SCS Number Failed	SCS Person-Years	SCS Event Rate (%)	IADP Number Interval	IADP Number Censored	IADP Number Failed	IADP Person-Years	IADP Event Rate (%)
[0,1)	1891	1205	71	902.30	7.87	314	191	5	173.59	2.88
[1,2)	615	310	144	369.77	38.94	118	81	2	72.57	2.76
[2,3)	161	123	38	59.14	64.26	35	35	0	16.26	0
Overall	**2667**	**1638**	**253**	**1331.21**	**19.01**	**467**	**307**	**7**	**262.42**	**2.67**

ANALYSIS 7

Interval	SCS Interval	SCS Censored	SCS Failed	SCS Years	SCS Rate (%)	IADP Interval	IADP Censored	IADP Failed	IADP Years	IADP Rate (%)
[0,1)	1891	704	71	1543.76	4.60	314	126	5	254.22	1.97
[1,2)	1116	573	138	754.07	18.30	183	95	2	131.65	1.52
[2,3)	405	367	37	190.53	19.42	86	86	0	46.82	0
[3,4)	1	1	0	0.03	0					
Overall	**3413**	**1645**	**246**	**2488.40**	**9.89**	**583**	**307**	**7**	**432.69**	**1.62**

ANALYSIS 8

Interval	SCS Interval	SCS Censored	SCS Failed	SCS Years	SCS Rate (%)	IADP Interval	IADP Censored	IADP Failed	IADP Years	IADP Rate (%)
[0,1)	1891	696	71	1547.32	4.59	314	117	5	260.61	1.92
[1,2)	1124	571	144	760.86	18.93	192	100	2	139.73	1.43
[2,3)	409	370	38	194.02	19.59	90	90	0	48.81	0
[3,4)	1	1	0	0.03	0					
Overall	**3425**	**1638**	**253**	**2502.23**	**10.11**	**596**	**307**	**7**	**449.14**	**1.56**

7.4. Hospitalization costs per implant

7.4.1. Data cleaning

To have a 2 month period of data available before every device implantation, data were withhold from 2006, March 1st . Data before 2006 were discarded because all one-day hospitalizations were missing from the database. Implants that were placed during the same stay were discarded (n=6), as well as 2 implants closely implanted that were competing for the same electrode hospitalization (n=2). Thirteen SCS implants with a reimbursed amount=0 for the device, were also rejected from the calculation (these implants could have been offered by the manufacturer during a warranty period). Finally a last SCS device was discarded that was implanted during a classic stay without any record of hospitalization lump sums.

A total of 2362 implants were kept, together with 1505 stays in the 2-month preceding period to be included in the hospitalization costs. In 2009, 261 SCS devices (including 10 rechargeables devices) and 36 pumps were included in the calculation.

7.4.2. Reconstruction of the part of the hospital financing related to an hospitalization stay in particular

In Belgium, hospital accommodation, emergency services including operating room, and nursing day activities are financed through the prospective budget that is fixed each semester for each hospital. [191] This budget is paid by two mechanisms. First, a fixed part is paid by monthly advances (provisional twelfths, not recorded in the Billing Data). Second, the variable part is paid by the RIZIV–INAMI by admission and per diem lump sums (recorded in the Billing Data along with number of days). As the variable part amounts only covers a part of the whole prospective budget of the hospital, the total amount financed by the Belgian authorities was reconstructed per stay, based on the list of so-called 100% (full) day prices published by the RIZIV–INAMI. Those full day prices, that vary according to the occupied bed type, were multiplied by the number of days spent in hospital per bed type. The result gives a proxy of the budget received by the hospital related to the hospitalization stay in particular.

7.4.3. Scenarios

Three scenarios were chosen to calculate the hospitalization costs. The cheapest one (1) included only the hospitalization during which the device was implanted (index hospitalizations). In the most expensive scenario (3), the hospitalization costs pertained to the whole device implantation episode, including the costs of the hospitalizations recorded in the two months preceding the device implantation date (in order to capture the four-week trial period). The in-between scenario (2), consisted in adding only the hospitalizations which were found related to the device therapy to the index hospitalization.

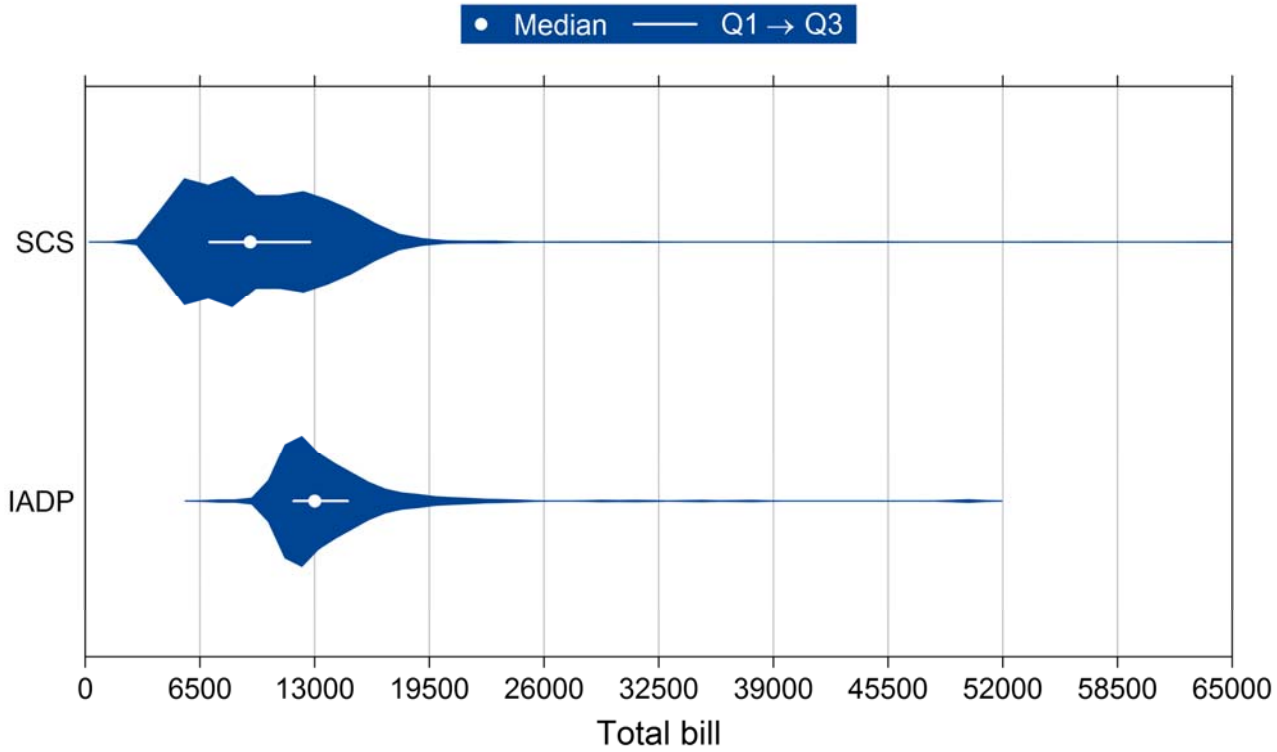
7.4.4. Results

Results for 2006-2008 are presented in Figure 19 after filtering for one SCS outlier (out of 1773). This amount is due to an hospitalization of 216 days in 2008 during which a SCS was implanted (total bill of this hospitalization= € 130 000).

Figure 19 – Total hospitalization costs and material costs per type of implants (2006-2008 and 2009)

Implant	2006-2008 Scenario 1	2006-2008 Scenario 2	2006-2008 Scenario 3	2009 Scenario 1	2009 Scenario 2	2009 Scenario 3
SCS						
N implants	1772			251		
N stays	1772	2245	2865	251	268	356
Total Bill	**9232** (SD=3636; median=8958)	**10024** (SD=4283; median=9353)	**10466** (SD=4502; median=9805)	**8672** (SD=3148; median=8173)	**8805** (SD=3340; median=8184)	**9280** (SD=3857; median=8369)
Material cost	**7600** (SD=2385; median=7489)	**7852** (SD=2566; median=7489)	**7868** (SD=2562; median=7489)	**7472** (SD=2621; median=7095)	**7511** (SD=2652; median=7095)	**7515** (SD=2651; median=7095)
Percentage Material	**82.30%**	**78.30%**	**75.20%**	**86.20%**	**85.30%**	**81.00%**
Rechargeable SCS						
N implants				10		
N stays				10	10	16
Total Bill				**19694** (SD=998; median=19912)	**19694** (SD=997; median=19912)	**19864** (SD=1014; median=20159)
Material cost				**18507** (SD=717; median=18596)	**18507** (SD=717; median=18596)	**18507** (SD=717; median=18596)
Percentage Material				**94.00%**	**94.00%**	**93.20%**
IADP						
N implants	292			36		
N stays	292	370	558	36	48	69
Total Bill	**13286** (SD=4256; median=12244)	**14138** (SD=4577; median=13008)	**15106** (SD=5425; median=13780)	**13313** (SD=1968; median=12731)	**14254** (SD=2758; median=13493)	**15248** (SD=3709; median=14194)
Material cost	**8859** (SD=820; median=9875)	**10009** (SD=827; median=10072)	**10014** (SD=815; median=10072)	**10066** (SD=282; median=9875)	**10107** (SD=296; median=10092)	**10113** (SD=299; median=10092)
Percentage Material	**66.70%**	**70.80%**	**66.30%**	**75.60%**	**70.90%**	**66.30%**

Figure 20 – Total hospitalization costs per type of implants (2006-2008 – scenario 2)



Line is delimited by the 1st and 3rd quartiles. Median is represented by a dot. Violin is drawn from the first to the last observation, depicting the density probability function of the data..

Table 93 – Parameters of the distribution of total bill components (2006-2008 – scenario 2).

Device therapy	Costs	N	Mean	Std Dev	Minimum	5th Pctl	25th Pctl	50th Pctl	75th Pctl	95th Pctl	Maximum
SCS	Total bill	1772	10024	4283	2798	5035	7037	9353	12739	16214	63765
	Hospital		1259	2151	47	101	285	836	1660	3510	40256
	Clinical biology		6	14	0	0	0	0	7	24	213
	Implants		7852	2566	2015	4598	4874	7489	9857	11875	21054
	Pharmaceuticals		171	143	0	6	54	154	224	393	2009
	Medical honoraria		736	600	63	326	429	559	920	1551	10818
	SPLR(*)		0	7	0	0	0	0	0	0	288
IADP	Total bill	292	14138	4577	7648	10938	11810	13008	14875	20594	49966
	Hospital		2716	3720	123	534	1075	1831	3199	7289	35821
	Clinical biology		16	43	0	0	1	7	13	55	494
	Implants		10009	827	5194	9875	9875	10072	10163	10768	14036
	Pharmaceuticals		272	532	0	66	159	182	249	435	6473
	Medical honoraria		1122	920	213	418	536	676	1584	2727	8103
	SPLR(*)		3	27	0	0	0	0	0	0	384

** SPLR: blood, plasma, maternal milk and radio-isotopes*

Table 94 – Parameters of the distribution of total bill components (2009 – scenario 2).

Device therapy	Costs	N	Mean	Std Dev	Minimum	5th Pctl	25th Pctl	50th Pctl	75th Pctl	95th Pctl	Maximum
SCS	Total bill	251	8805	3340	4470	4938	5861	8184	11055	15021	22740
	Hospital		652	1023	49	54	107	329	837	2173	9261
	Clinical biology		3	8	0	0	0	0	1	17	76
	Implants		7511	2652	3882	4598	4598	7095	9552	12151	14007
	Pharmaceuticals		119	305	0	6	18	129	148	257	4721
	Medical honoraria		520	289	187	208	363	472	579	1068	2161
	SPLR(*)		1	13	0	0	0	0	0	0	204
Rechargeable SCS	Total bill	10	19694	997	17354	17354	19196	19912	20367	20883	20883
	Hospital		574	419	54	54	118	664	736	1252	1252
	Clinical biology		1	3	0	0	0	0	0	10	10
	Implants		18507	717	17000	17000	18500	18596	19102	19378	19378
	Pharmaceuticals		105	49	17	17	75	123	131	156	156
	Medical honoraria		507	103	284	284	497	544	556	612	612
	SPLR(*)		0	0	0	0	0	0	0	0	0
IADP	Total bill	36	14254	2758	11192	11509	12024	13493	15174	20238	21099
	Hospital		2723	1883	367	681	1287	2300	3224	6890	8352
	Clinical biology		13	13	0	0	3	9	17	50	60
	Implants		10107	296	9875	9875	9875	10092	10163	10909	10931
	Pharmaceuticals		230	124	125	129	160	189	242	543	741
	Medical honoraria		1175	819	392	458	588	774	1697	2781	3644
	SPLR(*)		6	34	0	0	0	0	0	0	204

** SPLR: blood, plasma, maternal milk and radio-isotopes*

Table 95 – Length of stay of the SCS and IADP implantation hospitalizations (2006-2008) and 2009.

	Device type	N obs	Mean	Std Dev	Min	5th Pctl	25th Pctl	Median	75th Pctl	95th Pctl	Max
2006-2008	**SCS**	1772	2.6	6	1	1	1	2	3	7	156
	IADP	292	6.2	10.5	1	1	3	4	6	12	104
	Device type	**N obs**	**Mean**	**Std Dev**	**Min**	**5th Pctl**	**25th Pctl**	**Median**	**75th Pctl**	**95th Pctl**	**Max**
2009	**SCS**	251	1.8	2.0	1	1	1	1	2	5	20
	Rechargeable SCS	10	1.5	0.7	1	1	1	1	2	3	3
	IADP	36	5.4	3.6	1	1	3	5	7	14	18

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