New York Department of Health

Dossier Summary and Response

Topic: Implantable Infusion Pumps for Non-cancer Pain **Date**: December 17, 2015

Dossier Submission

Medtronic, Inc. submitted a dossier on implantable infusion pumps for chronic non-cancer pain on March 6, 2015. The dossier was completed in accordance with the Department's instructions and included 56 articles (52 summarized/reviewed) for review published between 1996 and 2014. Of the submitted articles, 41 were rated by the submitter as having good methodologic quality, 11 were rated fair quality, and one was rated poor quality. Four studies (Falco et al., 2013; Raffaeli et al., 2008; Wallace, Rauck, & Deer, 2010; Winkelmuller, Burchiel, & Van Buyten, 1999) were included in the dossier, but were not assessed. The submitted articles provided information on the effects of intrathecal drug devices used for treating chronic non-malignant pain. Other than pain, quality of life and disability outcomes were also reported. Additionally, studies addressed both device-related and medication-related harms of intrathecal drug therapy, and device-associated costs.

Dossier Review Process

The Center for Evidence-based Policy (CEbP) provided a review of the submitted dossier. Submitted articles were independently assessed for inclusion, methodological quality, and reported results. Literature searches of the MEDLINE (Ovid) database (no date limit) and CEbP's core sources[1] (a select group of resources considered high quality due to being independent and using systematic methods) were conducted to identify any additional relevant evidence.

Review Results

Evidence Evaluation – Included Studies

CEbP staff performed a search to identify any additional articles relevant to the topic. The search methodology is detailed in Appendix A. No date limit was applied to the search. When reviewing the studies either submitted with the dossier or identified by the subsequent search, only comparative studies were considered for evaluation of efficacy. Included studies were limited to English language, systematic reviews (SRs) with or without meta-analyses,

[1] CEbP core sources searched include Hayes, Inc., Cochrane Library (Wiley Interscience), the United Kingdom National Institute for Health and Care Excellence (NICE), the Blue Cross/Blue Shield Health Technology Assessment (HTA) program, the Veterans Administration Technology Assessment Program (VATAP), *BMJ Clinical Evidence*, the Canadian Agency for Drugs and Technologies in Health (CADTH), the Washington State Health Technology Assessment Program, the United States Preventive Services Task Force (USPSTF), and the Agency for Healthcare Research and Quality (AHRQ).

randomized controlled trials (RCTs), or observational studies. Case series were additionally considered to evaluate harms. In addition, only patient important outcomes have relevance for NY DOH. The rationale for study inclusion can be found in the New York Department of Health Dossier Methods Guidance (New York Department of Health, 2015). Exclusion criteria were selected prior to review of the studies, and study methods were assessed prior to review of outcomes to eliminate bias.

Exclusion criteria included:

- Original research with less than 10 participants
- Retrospective designs in which:
    - Study population was not drawn randomly or consecutively
    - Participants were required to recall their pre-intervention pain scores
- More than 15% of participants had cancer-related pain
- Less than 6 months of follow-up for efficacy outcomes (included for harms)
- Information from research study published more than once (only the highest quality article was included)
- Intervention other than permanent implanted pump. Examples include:
    - Intrathecal drug trial period with a temporary catheter only. A successful trial period is often reported as >50% pain improvement, and is often a clinical prerequisite to permanent implantation.
    - Comparative study of medications or device other than intrathecal infusion pump

A search of CEbP core sources identified two systematic reviews in addition to those submitted in the dossier (Hayes, 2014; Noble, 2008). The Medline (Ovid) database search identified 10 studies in addition to those provided by the submitter (listed in Appendix B). Of the 2,488 studies identified in the MEDLINE search, 133 were identified as potentially relevant. After review of the title and abstract, 41 studies were excluded based on sample size, four were excluded based on study design, 18 were excluded based on intervention, and 32 were excluded based on outcomes. Sixteen of the additional studies identified were also included in the dossier submission. The full text of 22 studies were reviewed, with 9 studies selected for final inclusion. Appendix B provides the rationale for study inclusion and exclusion based on full text review.

Review of the included dossier materials resulted in exclusion of 21 of the 56 submitted articles based on study design or population, intervention, or treatment under study (see Table 3 for a further description of studies and exclusion criteria). Table 1 includes a complete list of included articles, and associated methodological quality ratings, sample size and findings that were provided by the submitter or identified in the searches described above. Study quality was

rated by CEbP using the same quality assessment forms as provided by the submitter. Appendix C includes the both raters quality assessment for all included studies.

Evidence Review

This section provides an overview of included studies and a summary of the findings regarding effectiveness, harms and costs related to intrathecal pumps for non-cancer pain. The quality ratings included in this section refer to the ratings by the CEbP unless otherwise specified. Table 1 provides a further summary of the studies with more detail than included in the summary below.

Included Studies

Twelve SRs are included in this review. Four of the SRs were rated as having good methodological quality (Hayes Inc., 2014; Noble, Treadwell, Schoelles, & Sun, 2008; Noble et al., 2010; Turner, Sears, & Loeser, 2007), four were rated as having fair methodological quality (Duarte, Raphael, Southall, Baker, & Ashford, 2012; Falco et al., 2013; Hayek, Deer, Pope, Panchal, & Patel, 2011; Patel et al., 2009), and two were rated as having poor methodological quality (T. R. Deer, Levy, et al., 2012; T. R. Deer, Prager, Levy, et al., 2012a, 2012b; Narouze, Casanova, & Souzdalnitski, 2014). Two SRs were not included in the dossier submission, but were identified in the CEbP core search (Hayes Inc., 2014; Noble et al., 2008). These SRs included original research with a substantial degree of overlap. Table 1 lists references included in the review that were also submitted in the dossier or identified in the CEbP search. There was discordance among CEbP and submitter ratings for 78% of the SRs rated by both organizations.

One good quality (Raphael, Duarte, Southall, Nightingale, & Kitas, 2013), two fair quality (R. Rauck, Coffey, et al., 2013; R. L. Rauck et al., 2006), and one poor quality (Wallace et al., 2006) RCTs are included in this review, of which three were submitted in the dossier and one was identified through the CEbP MEDLINE® search (R. Rauck, Coffey, et al., 2013). None of these studies were included in the SRs, although Hayes (2014) summarized one RCT without including it in the evidence table (Raphael et al., 2013). There is discordance among the methodologic quality ratings between submitter and CEbP for 66% of the submitted studies.

Ten prospective cohort studies are included, of which one was rated as fair quality (Lara, Teixeira, & Fonoff, 2011) and the remaining were rated as poor quality (Anderson & Burchiel, 1999; T. Deer et al., 2004; Duse, Davia, & White, 2009; Hamza et al., 2012; Ilias, le Polain, Buchser, & Demartini, 2008; R. Rauck, Deer, et al., 2013; Rosen et al., 2013; Shaladi et al., 2007; Thimineur, Kravitz, & Vodapally, 2004; Wallace et al., 2008; Wesemann et al., 2014). Among the seven prospective cohort studies that were included in the dossier submission, there was discordance among all CEbP and submitter ratings. Three of the studies were identified in the

CEbP MEDLINE® search and not included in the dossier submission (Duse et al., 2009; Lara et al., 2011; R. Rauck, Deer, et al., 2013; Rosen et al., 2013).

Four fair quality (Grider, Harned, & Etscheidt, 2011; Hayek, Veizi, Narouze, & Mekhail, 2011; Kongkam et al., 2009; Mekhail et al., 2014) and three poor quality (Atli, Theodore, Turk, & Loeser, 2010; Coffey et al., 2009; Kim, Saidov, Mandhare, & Shuster, 2011) retrospective cohort studies were included. Submitter and CEbP quality ratings were discordant for 100% of the four submitted studies (Atli et al., 2010; Coffey et al., 2009; Hayek, Veizi, et al., 2011; Mekhail et al., 2014). Three of the retrospective cohort studies were identified in the CEbP MEDLINE® search and not included in the dossier submission (Grider et al., 2011; Kim et al., 2011; Kongkam et al., 2009). Most of the observational studies were included in one or more of the SRs described above.

Four poor quality case series (Fluckiger, Knecht, Grossmann, & Felleiter, 2008; Hayes, Jordan, Hodson, & Ritchard, 2012; Kamran & Wright, 2001; Maeyaert, Buchser, Van Buyten, Rainov, & Becker, 2003) were included to assess harms alone, and 75% of quality assessment ratings were discordant between the submitter and CEbP. All of the case series were submitted in the dossier.

Five fair quality (de Lissovoy, Brown, Halpern, Hassenbusch, & Ross, 1997; Dewilde, Verdian, & Maclaine, 2009; Guillemette, Witzke, Leier, Hinnenthal, & Prager, 2013; Kumar, Hunter, & Demeria, 2002; Thrasher & Fisher, 2013) and three poor quality (Bolash et al., 2015; Kumar, Rizvi, Bishop, & Tang, 2013) cost studies were included, of which two were identified by the CEbP MEDLINE® search (Biggs, Duarte, Raphael, & Ashford, 2011; Thrasher & Fisher, 2013). There was 100% discordance among quality ratings for the cost studies.

There are several common biases across the included studies. The majority of studies are non-comparative, have limited internal validity, are small, and are drawn from a single center which limits generalizability. In addition, there is a general association of authors with the device manufacturer or receiving funding from the device manufacturer.

Effectiveness

Pain outcomes

Most studies report pain using a numeric or visual analog scale, and pain is reported as average change and/or percent change from baseline. A greater than or equal to 30% change in pain is considered a clinically significant and moderately important change, and a greater than or equal to 50% change is considered a substantially important change (Hayes Inc., 2014; Raphael et al., 2013). All SRs reporting on pain outcomes report both clinically and statistically reductions in pain. Both short-term (less than or equal to 12 months) and long-term (greater than 12 months) outcomes were positive overall, with only one SR reporting negative findings from a

prospective cohort study comparing pump (n=38) and non-pump (n=31) patients (Patel et al., 2009). Overall, the individual studies were too heterogeneous in population type, methods, and reported outcomes such that outcome effects could not be combined (T. R. Deer, Prager, Levy, et al., 2012b; Falco et al., 2013; Hayek, Deer, et al., 2011; Hayes Inc., 2014; Noble et al., 2008; Noble et al., 2010; Patel et al., 2009; Turner et al., 2007).

One of the four included RCTs reported on pain outcomes. A small (n=15) randomized controlled trial, not included in the SRs above, randomized patients receiving intrathecal morphine for chronic non-cancer pain to a dose reduction or control arm. Those in the dose-reduction arm had significantly elevated pain, and 70% of participants in the dose reduction group dropped out due to inadequate pain control (Raphael et al., 2013).

Seven of the prospective cohort studies report pain outcomes, as measured by a visual analogue scale (VAS) or numeric rating scale (NRS) as the primary outcome. All studies present a statistically significant and clinically meaningful average reduction in pain over a 12 to 48 month period, depending on the study (see Table 1 for specific study outcomes) (Anderson & Burchiel, 1999; T. Deer et al., 2004; Duse et al., 2009; Hamza et al., 2012; Ilias et al., 2008; Lara et al., 2011; R. Rauck, Deer, et al., 2013; Rosen et al., 2013; Shaladi et al., 2007). One study that reported particularly strong improvements in pain assessed intrathecal opiates in the treatment of vertebral fracture over 12 months. However, the positive results may have been due to the natural progression of pain relief with healing of the fracture and not the use of an intrathecal pain pump (Shaladi et al., 2007).

Quality of Life

Four prospective non-comparative cohort studies and one comparative prospective cohort study (Thimineur et al., 2004) reported on quality of life. Hamza et al. (2012), a poor quality study, reported that mood, sleep, general activity, walking activity, and normal activity were all improved at 36 months. Mood and function scores were also improved in treatment groups compared to patients who either declined or failed a trial of intrathecal treatment (Thimineur et al., 2004). Quality of life was improved in the two other prospective cohort studies, and different measures were used (Duse et al., 2009; Shaladi et al., 2007).

Disability

Improved function was noted in most of the observational studies summarized by the Hayes (2014) (good quality) and Falco et al. (2013) (fair quality) SRs. Disability was not reported in a consistent manner across studies, making it difficult to determine the magnitude of impact.

Five prospective cohort studies reported improvements in functionality and disability scores. Different measures were used to report this outcome (T. Deer et al., 2004; Duse et al., 2009; Lara et al., 2011; R. Rauck, Deer, et al., 2013; Rosen et al., 2013; Thimineur et al., 2004).

Oral Pain Medications

One SR reported a reduction in complementary pain medications used among those treated with intrathecal drug therapy. However, the actual effective reduction could not be determined due to heterogeneity in patients, methods, and reporting (Noble et al., 2008).

One prospective cohort study required patients to wean off oral opiates with the exception of low dose as needed opiates at enrollment, and demonstrated significant reduction (from an average of 128 mg morphine daily to 4 mg daily) in oral opiate dose that was sustained over 36 months (Hamza et al., 2012).

Table 1. *Evidence Review – Included References*

Citation, Study Details	Dossier QA	CEbP QA	# of Studies (k) / Study Size (n)	Study Summary and Findings	Comments
Systematic Reviews					
Hayes (2014) Included Study Designs Observational	Not included	Good	k = 14 Total n = 1,017	Primary Outcome: Pain relief Significant (≥ 30%) improvement in pain reported from baseline to follow-up (20% to 67%) Secondary Outcomes: Improved disability/ functionality scores reported in 5 studies Improved QOL and satisfaction, and decreased systemic opiate dose were reported inconsistently in few studies Harms: Adverse medication events common, but not severe. Device-related complications common, revision in 3% to 40% of pts.	Studies are generally low quality and cannot be combined due to heterogeneity Overlapping studies[2]: (Anderson & Burchiel, 1999; Atli et al., 2010; Doleys, Brown, & Ness, 2006; Duse et al., 2009; Hamza et al., 2012; Kim et al., 2011; Lara et al., 2011; R. Rauck, Deer, et al., 2013)
Narouze et al. (2014) Included Study Designs Case series, case reports	Fair	Poor	k = 28 Total n = 80	SR on the complication of granuloma development post intrathecal implant Harms: 80 reports of granuloma development in 28 studies. A history of previous spinal cord injury or surgery was present in 68% of pts with intrathecal catheter granuloma, while 48% of pts with intrathecal catheter infusion pump had	Included for harms only Frequency of granuloma could not be calculated (no denominator) Overlapping studies: None

[2] Overlapping studies are those which are reviewed in the systematic review and were either included in this summary or the dossier submission.

Citation, Study Details	Dossier QA	CEbP QA	# of Studies (k) / Study Size (n)	Study Summary and Findings	Comments
				previous injury or surgery.	
Falco et al. (2013) Included Study Designs Observational	n/a[3]	Fair	k = 7 Total n = 830	Primary Outcome: Pain improvement Long-term (>12 months) pain improvement demonstrated in 6 of the studies, 3 showed significant improvement in short-term pain (≤ 12 months) Secondary Outcome: Improvement in functional scores in both short- and long-term demonstrated in 5/7 studies	Overlapping studies: (T. Deer et al., 2004; Hamza et al., 2012; Thimineur et al., 2004)
T. R. Deer, Levy, et al. (2012) Included Study Designs SRs, observational	Good	Poor	Unclear	SR on harms informed guidelines. Much of literature focused on adverse effects in preclinical (animal) studies Conclusion: Complications of intrathecal drug devices are relatively common and can be severe. Appropriate pt selection and follow-up is important.	Guidelines developed by expert panel Review presented in narrative form Overlapping studies: (Atli et al., 2010; Coffey et al., 2009; Kongkam et al., 2009; Raffaeli et al., 2008; Saltari et al., 2007; Shaladi et al., 2007; Turner et al., 2007)[4]
T. R. Deer, Prager, Levy, et al. (2012b) Included Study Designs SRs, observational	Good	Poor	Unclear	SR informed guidelines developed by an expert panel, supports recommendation to use morphine with or without bupivacaine or ziconotide as first line for the treatment of non-neuropathic pain, and morphine, fentanyl, ziconotide, or hydromorphone for neuropathic pain.	SR with high risk of bias informed guidelines developed by expert panel Overlapping studies: (Atli et al., 2010; Coffey et al., 2009; Kongkam et al., 2009; Raffaeli et al., 2008; Saltari et al., 2007; Shaladi et al., 2007; Turner et al., 2007; Wallace et al., 2008)[5]

[3] Systematic review included in dossier submission, but not assessed for methodological bias
[4] Saltari et al. (2007) and Shaladi et al. (2007) include same study population

Citation, Study Details	Dossier QA	CEbP QA	# of Studies (k) / Study Size (n)	Study Summary and Findings	Comments
T. R. Deer, Prager, Levy, et al. (2012a) Included Study Designs Case series, case reports	Good	Poor	Unclear	SR of granuloma associated with implanted intrathecal catheter informed guidelines Conclusion: Intrathecal granulomas are more common in pts receiving higher doses of opiates, and in those whom the dose is rapidly increased. Granulomas are also associated with administration of high drug concentrations at low flow rates and increased duration of drug infusion. Pt factors that may increase the risk include history of granuloma formation and diseases that result in low cerebral spinal fluid flow rates around catheter tip (severe cervical stenosis, traumatic spinal cord injury).	Included for harms only Frequency of granuloma could not be calculated (no denominator) Overlapping studies: None
Duarte, Raphael, Southall, et al. (2012) Included Study Designs Case reports	Good	Fair	n = 56	SR of case reports of granulomata were compared to a control group. Summary of case reports made up the "case" population for a case-control study. Conclusion: There is a significantly higher odds of developing granulomata among those receiving a higher dose and concentration of morphine	Included for harms only Frequency of granuloma cannot be determined due to lack of denominator Overlapping studies: None
Hayek, Deer, et al. (2011) Included Study Designs SRs,	Good	Fair	k = 15 Total n = 1,375	Primary Outcome: Pain reduction 8 studies report statistically significant outcome of ≥ 30% pain relief and 7 studies report statistically significant outcome of ≥50% pain relief at 12 months	Overlapping studies: (Anderson & Burchiel, 1999; Atli et al., 2010; T. Deer et al., 2004; Duse et al., 2009; Ilias et al., 2008; Noble et al., 2010; Patel et al., 2009; Shaladi et al., 2007; Thimineur et al., 2004;

Citation, Study Details	Dossier QA	CEbP QA	# of Studies (k) / Study Size (n)	Study Summary and Findings	Comments
observational				Harms: Adverse events reported included device failure or malfunction, catheter migration, infection, seroma, hematoma, granuloma, confusion, and medication effects	Turner et al., 2007)
Noble et al. (2010) Included Study Designs Observational	Good	Good	k = 10 Total n = 231	Primary Outcome: Pain reduction The average pooled pain score was reduced significantly (from 8.7 to 4.5) from baseline to the longest time of follow-up (6 to 29 months) for the 201 pts who continued treatment. 7 studies (n=151) reported a result of >50% pain reduction, and the average proportion of pts meeting >50% pain reduction was 44.5%. Harms: Adverse events were common and 9% of participants discontinued treatment due to adverse events. Ineffective treatment resulted in discontinuation of therapy in 8% of participants.	There is significant heterogeneity and inconsistent outcome reporting among studies Pooled effects should be interpreted with caution Overlapping studies: (Anderson & Burchiel, 1999; Shaladi et al., 2007; Thimineur et al., 2004)
Patel et al. (2009) Included Study Designs Observational	Good	Fair	k = 4 Total n = 386	Primary Outcome: Pain reduction Two studies demonstrated ≥ 50% pain reduction in 74% to 82% of participants at 12 months. One study reported negative findings. One study reported additional benefits of intrathecal morphine + bupivacaine compared to intrathecal morphine alone. There is insufficient summary of secondary outcomes and harms.	One study that was excluded from the review (Shaladi et al., 2007) is included in the evidence table. This study had 100% achievement in ≥ 50% pain reduction. The search strategy is not published in detail, and the number of studies included seems small for dates searched. Authors provide a strong recommendation for the use of intrathecal infusion pumps with low quality evidence.

Citation, Study Details	Dossier QA	CEbP QA	# of Studies (k) / Study Size (n)	Study Summary and Findings	Comments
					Overlapping studies: (Shaladi et al., 2007; Thimineur et al., 2004)
Noble et al., (2008) Included Study Designs Observational	Not included	Good	k = 13 Total n = 413	Primary Outcome: Pain reduction Pain score decreased from 8.7 at baseline to 4.3 at longest follow-up. Results on 50% pain reduction varied from 11% to 100%. Secondary Outcomes: 3% to 13% of pts discontinued therapy due to inadequate pain relief. 9 studies (n=367) reported a decrease in use of other pain medications at last follow-up. There was insufficient evidence to determine impact on quality of life or functionality. Harms: 0% to 15% of pts discontinued therapy due to medication adverse events. There were no adverse medicine events, however device failure that required re-operation occurred in 9% to 42% of participants. 975 reports were isolated from the MAUDE database. There were 15 deaths reported, and 5 due to overdose. The highest number of complications reported were for infection, inflammatory masses, and paralysis. There was insufficient data to perform a cost analysis. Conclusion: Low quality evidence supports	Cannot conclude magnitude of effect due to study heterogeneity SR is relatively outdated Overlapping studies: (de Lissovoy et al., 1997; T. Deer et al., 2004; Kumar et al., 2002; Shaladi et al., 2007; Thimineur et al., 2004)

Citation, Study Details	Dossier QA	CEbP QA	# of Studies (k) / Study Size (n)	Study Summary and Findings	Comments
				significant pain relief with intrathecal infusion pumps for chronic non-cancer pain, however there is insufficient evidence to predict magnitude of effect. Evidence on pt criteria that would influence outcomes is lacking, which would be useful for pt selection.	
Turner et al. (2007) Included Study Designs Observational	Good	Good	Effectiveness k = 6 Total n = 258 Harms k = 10 Total n = 342	Primary Outcome: Pain reduction 35% to 56% of participants achieved >50% pain relief at 6 months, and 30% to 44% did so at 12 and longer follow-ups. Harms: Common side effects included nausea, urinary retention, pruritis, pump malposition, and wound infection. On average across studies, 27% had pump revision surgery and 5% had their pump removed permanently. The average study length was 27 months.	Studies are heterogeneous in pt characteristics and outcomes. Authors concluded studies are low quality evidence, and further research (specifically RCTs) are needed to determine effectiveness. There was not a long-enough follow-up to be certain all harms were captured. Overlapping studies: (Anderson & Burchiel, 1999; T. Deer et al., 2004)
Randomized Controlled Trials					
Raphael et al. (2013) Study length 10 weeks Indication Non-cancer pain Intrathecal Medication	Good	Good	n = 15	Primary Outcome: Pain reduction 15 pts receiving morphine via intrathecal infusion pump were randomized to have a dose reduction of 20% every week or have no dose reduction. Pain was significantly elevated in the dose reduction group, but not in the control group. 70% of participants in intervention group dropped out due to increased pain and study was ended early.	The groups were comparable at baseline, and there were no significant differences in pt characteristics among those who dropped out

Citation, Study Details	Dossier QA	CEbP QA	# of Studies (k) / Study Size (n)	Study Summary and Findings	Comments
Morphine ± adjuvant medication					
Rauck et al. (2006) Study length 3 weeks Indication Chronic non-cancer pain Intrathecal Medication Ziconotide	Good	Fair	n = 220	Harms: Adverse events were common. Dizziness, confusion, abnormal gait, and memory impairment were statistically significantly more common among those receiving ziconotide intrathecally compared to placebo. Discontinuation rates for treatment groups due to adverse events were comparable (5.4% and 4.6% percent).	Efficacy outcomes excluded as follow-up was <6 months.
Rauck et al. (2013) Study length 22 days Indication Chronic pain NOS Intrathecal Medication Gabapentin	Not included	Fair	n = 170	Harms: There were 130 gabapentin-related adverse events in 71 pts (41.8%), and 123 device-related adverse events in 162 pts (94.7%). During the pre-randomization interval 57 (33.3%) experienced device-related complications prior to administration of study drug. Among this group, the most common adverse events were lumbar puncture headache and pain as complication of procedure. Two pts experienced pump-site infection that resulted in removal and discontinuation of the study. Common drug-related adverse events were nausea, somnolence, headache, dizziness,	Included for harms only due to study duration of <6 months.

Citation, Study Details	Dossier QA	CEbP QA	# of Studies (k) / Study Size (n)	Study Summary and Findings	Comments
				fatigue, and peripheral edema.	
Wallace et al. (2006) Study length 6 days Indication Chronic non-cancer pain Intrathecal Medication Ziconotide	Good	Poor	n = 264	Harms: Pts receiving intrathecal ziconotide reported statistically significantly more adverse events. Dizziness was the most common adverse events, reported in 54% of participants. Other common adverse events, which were statistically significantly more common than in the placebo group included: body pain, nausea, vomiting, abnormal gait, nystagmus, lazy eye, and urinary retention.	Efficacy outcomes excluded as follow-up <6 months The study protocol was adjusted mid-study due to adverse events associated with higher dose escalations of ziconotide
Prospective Cohort Studies[4]					
Anderson and Burchiel (1999) Study length 24 months Indication Non-cancer pain Intrathecal Medication Morphine	Good	Poor	n = 30	Primary outcome: Pain (VAS score) 1/3 of pts experienced >50% improvement in pain by VAS score at 24 months. Close to half experienced >25% pain relief at 24 months. Secondary outcome: Intrathecal morphine dose Morphine dose increased from 1.96 ±1.75 mg per day at baseline to 14.59 ± 20.52 mg per day at 24 months Harms: Device related complications included subdural puncture headache (8%), complications requiring repeat operation (20%). Intrathecal catheter-related complications included migration (8%), obstruction (4%), and seroma	Prospective cohort with no control 33% lost to follow-up Potential confounding factors not considered in analysis, including quantification of oral analgesics Single-center location limits generalizability

[4] All prospective cohort studies are non-comparative unless noted in the comments section.

Citation, Study Details	Dossier QA	CEbP QA	# of Studies (k) / Study Size (n)	Study Summary and Findings	Comments
				formation (8%). Pump malfunction occurred in 8% of pts. A programming error resulted in a fast infusion rate and hospitalization for one pt due to systemic drug effects. Common medication side-effects were constipation, nausea, lethargy, pruritus, and mental status change. One pt discontinued the study due to inadequate pain relief.	
T. R. Deer et al. (2004) Study length 12 months Indication Chronic low back pain Intrathecal Medication Morphine only in 81% of test pts	Fair	Poor	Temporary catheter n = 166 Implanted n = 136	Primary outcome: Pain (numeric rating) Numeric back pain ratings declined by 48% at 12 months, numeric leg pain ratings declined by 32% at 12 months Secondary outcomes Overall pain ratings declined by 58% at 6 months and 62% at 12 months Average Oswestry Disability Score decreased from 44.8 to 31.0 at 12 months 65% of participants reduced their systemic opiate use at 6 months Harms: Adverse events were recorded in 17% of participants, and 15% required surgical repair. Medication reaction was recorded in 5.1% of participants.	Among those with intrathecal trial dosing, 88% had IDDS implanted Among those implanted, 47% were lost to follow-up Outcomes were not recorded for those lost to follow-up There is bias in favor of treatment due to these factors
Duse et al. (2009) Study length	Not included	Poor	Temporary Catheter n = 42	Primary Outcome: Pain (VAS score) Average pain score decreased from 90 mm to 30 mm on VAS, and remained at 30 mm at 24	Outcomes of pts who were not implanted were not gathered It is unclear if all 30 implanted pts

Citation, Study Details	Dossier QA	CEbP QA	# of Studies (k) / Study Size (n)	Study Summary and Findings	Comments
24 months Indication Chronic non-cancer pain Intrathecal Medication Morphine			Implanted n = 30	months Secondary Outcomes Qualitative pain assessment by McGill Pain Questionnaire progressively improved throughout the study Function also improved in participants Harms: Not assessed	completed the study
Hamza et al. (2012) Study length 36 months Indication Chronic non-cancer Pain Intrathecal Medication Morphine	Good	Poor	Temporary Catheter n = 61 Implanted n = 58	Primary Outcome: Pain (Brief Pain Inventory) Average and worst pain scores halved at 6 months and remained low at 36 months. There were also significant improvements in general activity, walking activity, and normal work. Mood and sleep were also improved significantly. Secondary Outcome: Oral opiate use Mean opiate dose decreased from 128 mg morphine daily to 4 mg morphine daily at 3 months Harms: Adverse events included wound infection (5%), pruritus (5%), peripheral edema (3%), and seroma (3%)	Participants were required to wean down on oral opioids prior to the study Only low doses of oral morphine as needed were used throughout the study period
Lara et al. (2011) Study length 48 months	Not included	Fair	Temporary Catheter n = 78 Implanted	Primary outcome: Pain (VAS) Pain intensity was recorded as an 8.1 to 10 cm on VAS at baseline in more than half of the participants, and was less than 4.0 cm in half of	Some pts are treated with bolus and others with continuous infusion, and the number in each group is unclear Reasons for unsuccessful intrathecal

Citation, Study Details	Dossier QA	CEbP QA	# of Studies (k) / Study Size (n)	Study Summary and Findings	Comments
Indication Failed back surgery syndrome Intrathecal Medication Morphine			n = 30	the participants at 48 months Secondary outcomes Significant improvement in McGill Pain Questionnaire descriptors, quality of life by SF-36 questionnaire averaged 30.8 at baseline to 49.4 at 48 months Improvement in all domains of the "Treatment Outcomes in Pain Survey", except for objective work disability The percent of pts using systemic opiates declined by more than half Harms: 1 case of bacterial meningitis, and 1 pt who exhibited compulsive behavior for opiate intake. 12 (15%) pump or catheter revisions of which 2 were due to infection, and 10 were due to mechanic problems or replacement of the catheter.	morphine trailing are not recorded
R. Rauck, Deer, et al. (2013) Study length 12 months Indication Chronic pain Intrathecal Medication	Not included	Poor	n = 110	Primary Outcome: Pain (VAS and numeric score) Significant improvements in pain as measured by numeric rating scale (-2 points) and VAS (-20 mm) at 6 and 12 months Secondary outcome: Disability Significant improvement in Oswestry Disability Index (-10 points) Harms: 18 pts had one or more catheter complications, 18 had one or more surgical	3% of participants had cancer pain Only 55% of participants completed study at 12 months, and analysis was per protocol, placing study at high risk of bias in favor of intervention

Citation, Study Details	Dossier QA	CEbP QA	# of Studies (k) / Study Size (n)	Study Summary and Findings	Comments
Morphine				revisions, 8 had catheter migrations, 6 had pump positioning complications, 6 had implant site infections, and 2 had catheter occlusions	
Shaladi et al. (2007) Study length 12 months Indication Vertebral fracture Intrathecal medication Morphine	Good	Poor	n = 24	Primary outcome: Pain (VAS) Mean pain decreased on the VAS from 8.7 cm to 1.9 cm at the end of one year Secondary outcome: Function The mean functional score (QUALEFFO) decreased from 114.7 at baseline to 79.1 at 12 months Harms: 4 pump-related complications: 1 wound infection, 2 catheter dislocations, and 1 participant had delayed healing. 3 participants experienced nausea.	Natural improvement in vertebral fracture over the course of the year is expected and without comparator the results cannot be attributed to the pump
Thimineur et al. (2004) Study length 36 months Indication Chronic non-cancer pain Intrathecal medication Morphine	Good	Fair	n = 147 (Pump recipient group [88], non-recipient group [88], new pt group [pump recipient, but at later enrollment] [59])	Two cohorts receiving intrathecal morphine was compared to cohort who qualified for but did not receive pump implantation Primary Outcome: Pain (VAS) Pain decreased by over 2 cm in the pump recipient and new pt group. Pain increased by 0.5 cm in the non-recipient group. Secondary Outcomes The average McGill Pain Questionnaire score decreased from 40 to 33 and from 31 to 25 in recipients and new pts, respectively. The mean score increased from 39 to 44 in the non-	A relative strength of the study is a comparison group drawn from the same population as the treatment group who did not have an intrathecal pump placed

Citation, Study Details	Dossier QA	CEbP QA	# of Studies (k) / Study Size (n)	Study Summary and Findings	Comments
				recipient group. Mean Oswestry Disability Survey scores increased from 29 to 31 in the non-recipient group and decreased from 32 to 27 and 21 to 15, respectively in the pump recipient and new pt groups. Beck Depression Inventory Scores decreased by 5 points in both the recipient and new pt groups and increased by 5 points in the non-recipient group. Mean oral opiate dose decreased by half in the pump recipient group and increased by over 30% in the non-recipient group. Transdermal fentanyl dosing decreased by more than half in the pump recipient group and doubled in the non-recipient group. In the non-recipient group, there were 321 trigger point injections in 19 pts, compared to 45 trigger point injections in 15 pts in the pump recipient group. The study uses additional scales to report similar outcomes. All outcomes reported here are statistically significant. <u>Harms:</u> Frequencies of adverse events not reported	
Wallace et al.	Good	Poor	n = 644	<u>Harms:</u> Almost half of pts permanently	Included for harms only as average follow-

Citation, Study Details	Dossier QA	CEbP QA	# of Studies (k) / Study Size (n)	Study Summary and Findings	Comments
(2008) Study length 12 months Indication Chronic pain Intrathecal medication ziconotide				discontinued therapy due to adverse events, and 12% temporarily discontinued therapy. Cognitive dysfunction, psychiatric changes, headache, nausea, and catheter complications were the most common reasons for discontinuation.	up <6 months Only 18.5% of pts were receiving ziconotide at one year 2.5% of pts had cancer-related pain
Wesemann et al. (2014) Study length 12 months Indication Spasticity, pain, or both Intrathecal Medication Not specified/ likely multiple	Good	Poor	n = 82	Harms: 16% of pts had severe system-related events that required reoperation or hospitalization for medication adjustment. 58 system-related events in 38 pts. The most common system-related events were implant site effusion (14%), lumbar puncture headache (10%), catheter dislodgment (6%), implant site inflammation (5%), catheter break or cut (4%), and implant site infection (4%). 66 events in 32 pts related to medical treatments (both intrathecal and non-intrathecal).	Included for harms only Other outcomes are not pt-oriented 54% of pts had spasticity without pain
Retrospective Cohort Studies[5]					
Alti et al. (2010) Study length	Good	Poor	n = 57	Primary outcome: Pain (VAS) 67% of pts had ≥30% improvement in pain at first pump refill, while only 37% had this level of	Efficacy results should be interpreted with caution due to exclusion of 25% of pts

[5] All retrospective cohort studies include only one cohort

Citation, Study Details	Dossier QA	CEbP QA	# of Studies (k) / Study Size (n)	Study Summary and Findings	Comments
36 months Indication Chronic pain Intrathecal Medication Multiple and not specified				improvement at 3 years. 47% of participants had >50% improvement in pain at first refill, and only 18% had this level of pain improvement at 3 years. Secondary outcomes Oral opiate doses decreased 69% at one year, and this reduction was maintained at 3 years. Intrathecal opiate dose increased from baseline average of 6.5 mg/day to an average of 12.2 mg/day at 3 years. 24% of pts had treatment failure, and 20% had their pumps removed. Harms: Complications included wound infection (8.8%), catheter migration (5.3%), intrathecal granuloma (3.5%), seroma (3.5%), and pump malposition (3.5%)	
Coffey et al. (2009) Study length 12 months Indication Non-cancer pain Intrathecal Medication Opiates	Fair	Poor	n = 61,228 intrathecal drug device implants and 83,163 spinal cord stimulator implantations	Harms: The 3-day post-intrathecal drug device implant mortality rate is 0.88/1000, 8x higher than the 3-day mortality rate after spinal cord stimulator implant. The ratio of observed to expected deaths for the intrathecal drug device population was 7.5 at 3 days, 3.4 at 30 days, and 2.7 at one year, indicating that deaths are higher than would be normally be expected in the population.	This study only addressed harms Deaths may be overestimated due to inability to assess confounding factors from the registry data It is unclear if the spinal cord stimulator and intrathecal drug therapy groups are sufficiently comparable

Citation, Study Details	Dossier QA	CEbP QA	# of Studies (k) / Study Size (n)	Study Summary and Findings	Comments
Grider et al. (2011) Study length 12 months Indication Chronic non-cancer pain Intrathecal Medication Opiates	Not included	Fair	Temporary Catheter n = 22 Implanted n = 20	Primary outcome: Pain (VAS) Pain improved from 7.2 ±1.1 cm pre-implant to 3.9 ±2.6cm Secondary Outcome: Intrathecal morphine dose Effective analgesia was achieved at 50 µg of morphine per day for 3 pts, 100 µg daily for 7 pts, 200 µg daily for 8 pts, and 400 µg daily for 2 pts Harms: Not assessed	All pts weaned off oral opioids prior to implantation Two pts did not tolerate intrathecal opioids due to urinary retention
Hayek, Veizi, et al. (2011) Study length 12 months Indication Chronic non-cancer pain Intrathecal Medication Opiates alone or in combination with clonidine, bupivacaine, and/or ziconotide	Good	Fair	n=135	Primary Outcome: Pain (numeric rating scale) Pain improved significantly from 7.26 ± 1.7 at baseline to 5.4 ± 1.9 at 12 months. The average decrease in pain reduction was close to 30%. At 12 months, 25% of adults > 50 years had a numerical rating scale that was 50% improved from baseline, compared to 10% of younger participants. Secondary Outcomes: Intrathecal opiate doses increased by an average of 750% in pts ≤50 years compared to 195% in pts >50 years. Oral pain medication dose statistically significantly declined by an average of more than half in older pts throughout the course of the study, but remained stable in younger pts.	This study retrospectively reviewed one cohort and compared age groups within the cohort

Citation, Study Details	Dossier QA	CEbP QA	# of Studies (k) / Study Size (n)	Study Summary and Findings	Comments
				Harms: Not assessed	
Kim et al. (2011) Study length 12 months Indication Post-laminectomy syndrome Intrathecal Medication Opiates alone or in combination or ziconotide	Not included	Poor	n = 35	Primary Outcome: Pain (VAS) Mean change in VAS at one year was 26%. Pts with higher intrathecal trial doses had less pain relief at one year. Pts had more pain improvement at the end of one year with increasing age. Secondary Outcome: Medication change (yes/no) Over half of pts required a change in opiate dose or addition of adjuvant intrathecal medications Harms: Not reported	Descriptive retrospective cohort without comparator
Kongkam et al. (2009) Study length 12 months Indication Chronic pancreatitis Intrathecal Medication Multiple	Not included	Fair	n = 13	Primary Outcome: Pain score The mean pain score prior to implantation was 8.3, and this decreased to 2.7 at one year Secondary Outcomes Median oral narcotic dose decreased from 338 mg to 40mg morphine equivalents daily. 15% pts were considered failures for continuing to require high dose oral narcotics for pain treatment. One pt (8%) returned to full time work. 69% pts remained active in activities of daily living, and 15% were never able to resume activities.	Retrospective single arm cohort of pts with chronic pancreatitis Unclear what tool was used to measure pain

Citation, Study Details	Dossier QA	CEbP QA	# of Studies (k) / Study Size (n)	Study Summary and Findings	Comments
				Harms: 4 pts (31%) experienced pump failure at 31, 68, 79, and 84 months of follow-up. 15% developed meningitis, 1 with perispinal abscess. 1 pt (8%) experienced a cerebral spinal fluid leak requiring laminectomy.	
Mekhail et al. (2014) Study length 24 months Indication Chronic non-cancer Pain Intrathecal Medication Opiates	Good	Fair	n = 139	Primary Outcome: Dose increase Pts with neuropathic pain had a 30% higher annual rate of opiate dose escalation compared to pts with non-neuropathic pain Secondary Outcome: Pain reduction Pain reductions measured by change in VAS score was not different based on pain type Harms: Not reported	One cohort Assessed factors related to differences in intrathecal dose escalation
Case Series (harms only)					
Fluckiger et al. (2008) Study Length Review over 12 year period Indication Spasticity and chronic pain Intrathecal	Fair	Poor	n = 100	Harms: The incidence of device complications requiring surgical correction was 10.5% per year (excluding infection and pump replacement due to battery exhaustion). All infections occurred within the first three months of the original pump placement.	19% of pts had IDDS implanted for pain, and other reasons for implantation were spinal cord injury, cerebral palsy, and multiple sclerosis

Citation, Study Details	Dossier QA	CEbP QA	# of Studies (k) / Study Size (n)	Study Summary and Findings	Comments
Medication Multiple					
Hayes et al. (2012) Study Length Review over 13 year period Indication Chronic non-cancer pain Intrathecal Medication Opiate + clonidine	Poor	Poor	n = 25	Harms: This study enrolled participants from an area where the pain clinic was discontinuing intrathecal drug device management. 67% of participants stopped intrathecal therapy electively, and 29% stopped due to complications.	Retrospective survey data post-explant with 38% drop-out rate
Kamran and Wright (2001) Study Length Review over 8 year period Indication Chronic non-cancer pain and spasticity Intrathecal Medication Multiple	Fair	Poor	n = 122 reviewed; 97 included	Harms: 77% of participants had pharmacologic side effects. 3% had superficial infections, and 3% had more serious infections. Catheter-related equipment failure occurred in 16.5% of participants, including spinal headache in 3%. Pump-related failure occurred in 2%, and programming errors in 2%. Distorted body image occurred in 3%.	Retrospective review 20% excluded due to incomplete data Indication only reported for 50% of pts, and spasticity was cause of pump placement in 4% of those

Harms

Adverse events are not consistently reported among studies. Commonly reported adverse events include device failure or malfunction, migration of the catheter, infection, seroma, hematoma, granuloma, and medication side effects (Hayek, Deer, et al., 2011). The Hayes SR (2014) reported reoperation in 3% to 40% of patients. An additional good quality SR (Noble et al., 2010) reported the following statistics from studies reporting on select outcomes: 8.9% (95% CI: 4.0 to 18.6%) of participants discontinued treatment due to adverse events, and 7.6% (95% CI: 3.7 to 14.8%) discontinued therapy due to inadequate treatment. A good quality SR reported pump revision surgery occurred in an average of 27% of patients, and 5% had the pump permanently removed (Turner et al., 2007). Intrathecal catheter granuloma may be more common in those with previous spinal cord surgery based on a poor quality SR (Narouze et al., 2014). An additional poor quality SR identified rapid dose escalation, high opiate dose, high drug concentrations at low flow rates, and factors decreasing cerebral spinal fluid flow rates around the catheter tip as risk factors for intrathecal granuloma development (T. R. Deer, Prager, Levy, et al., 2012a). A fair quality SR of case reports was used to create a case population and inform a case-control study that identified high intrathecal morphine dose as an additional risk factor for intrathecal granuloma (Duarte, Raphael, Southall, et al., 2012). A poor quality SR also cited respiratory depression and hormonal suppression as important risks to consider (T. R. Deer, Levy, et al., 2012) in the application of implantable infusion pumps.

Three RCTs addressed adverse effects related to intrathecal treatment of pain. One trial studied the effects of intrathecal gabapentin, and reported device-related complication in 33.3% of participants (R. Rauck, Coffey, et al., 2013). Lumbar puncture headache and procedural pain were the most commonly reported acute side effects. Pump site infection and removal occurred in 1.5% of participants. Drug-related side effects included nausea, somnolence, headache, dizziness, fatigue, and peripheral edema. Two RCTs compared intrathecal ziconotide (a selective N-type calcium channel blocker) to placebo and found dizziness was the most common adverse effect (R. L. Rauck et al., 2006; Wallace et al., 2006). Abnormal gait, memory impairment, confusion, urinary retention, nausea, and vomiting were also reported.

Observational studies did not report adverse events in a consistent manner, and due to variability in length of studies and devices used, these data cannot be combined to estimate harms in an accurate or precise manner. Medication-related side effects were common and included nausea, pruritis, and peripheral edema. Commonly reported device-related adverse events are summarized in Table 2.

On December 9, 2015, CEbP staff searched the U.S. Food and Drug Administration's Manufacturer and User Facility Device Experience (MAUDE) database for reports on device injuries, malfunctions, and deaths of implantable infusion pumps. Since November 6, 2015,

there were over 500 reports which was inclusive of injuries, malfunctions and deaths. Since January 5, 2010, over 500 deaths related to implantable infusion pumps have been reported (U.S. Food and Drug Administration, 2015).

Table 2. *Frequency of Device-Related Adverse Events from Observational Studies*

Adverse event	Frequency	Citations and Study Size (n)
Prospective cohort studies		
Catheter complications NOS	14 to 16%	Rauck, Deer, et al. (2013) (n=110) Wallace et al. (2008) (n=644)
Catheter migration	6 to 8%	Anderson and Burchiel (1999)(n=30) Rauck, Deer, et al. (2013)(n=110) Shaladi et al. (2007) (n=24) Wesemann et al. (2014) (n=82)
Catheter obstruction	2 to 4%	Anderson and Burchiel (1999) (n=30) Rauck, Deer, et al. (2013) (n=110)
Catheter break or cut	4%	Wesemann et al. (2014) (n=82)
Pump malfunction	8 to 9.5%	Anderson and Burchiel (1999) (n=30) Wallace et al. (2008) (n=644)
Pump positioning complication	5%	Rauck, Deer, et al. (2013 (n=110)
Meningitis or wound infection	2 to 5.5%	Hamza et al. (2012) (n=58) Lara et al. (2011) (n=78) Rauck, Deer, et al. (2013) (n=110) Shaladi et al. (2007) (n=24) Wesemann et al. (2014) (n=82)
Seroma	6 to 8%	Anderson (1999) (n=30) Hamza (2012) (n=58)
Delayed healing	4%	Shaladi, 2007 (n=24)
Subdural puncture headache	8 to 15%	Anderson (1999) (n=30) Wallace (2008) (n=644) Wesemann (2014) (n=82)
Repeat operation	2 to 20%	Anderson (1999) (n=30) Deer (2004) (n=136) Lara (2011) (n=78)
Drug overdose due to	3.3%	Anderson (1999) (n=30)

Adverse event	Frequency	Citations and Study Size (n)
programming error		
Retrospective cohort studies		
Mortality	3-day mortality rate: 0.88/1000 Observed to expected mortality ratio: 7.5 at 3 days, 3.4 at 30 days, 2.7 at 1 year	Coffey et al. (2009) (n=61,228)
Treatment failure	15 to 24%	Alti et al. (2010) (n=57) Kongkam et al. (2009) (n=13)
Pump removal	20%	Alti et al. (2010) (n=57)
Wound infection	9%	Alti et al. (2010) (n=57)
Meningitis	15%	Kongkam et al. (2009) (n=13)
Catheter migration	5%	Alti et al. (2010) (n=57)
Pump malposition	3.5%	Alti et al. (2010) (n=57)
Pump failure	31% (occurring between 31 and 84 months)	Kongkam et al. (2009) (n=13)
Cerebral spinal fluid leak	8%	Kongkam et al. (2009) (n=13)
Seroma	3.5%	Alti et al. (2010) (n=57)
Granuloma	3.5%	Alti et al. (2010) (n=57)
Case series		
Device complications	58%	Fluckiger et al. (2008) (n=100)
Device complications requiring surgical correction	10.5% per year over 5.5 years	Fluckiger et al. (2008) (n=100)
Pump or catheter infections	6 to 8%	Fluckiger et al. (2008) (n=100) Kamran and Wright (2001) (n=97)
Pump changes	64 changes among 100 patients over 5.5 years	Fluckiger et al. (2008) (n=100)
Pump failure	2%	Kamran and Wright (2001) (n=97)
Spinal headache	3%	Kamran and Wright (2001) (n=97)
Catheter-related equipment failure	16.5%	Kamran and Wright (2001) (n=97)
Programming errors	2%	Kamran and Wright (2001) (n=97)

Evidence Evaluation – Excluded Studies

Table 3 provides exclusion criteria for submitted articles that were not included in this evaluation.

Table 3. *Submitted References – Reason for Exclusion*

Citation	Exclusion Criteria
T. R. Deer, Prager, Levy, Burton, et al. (2012)	Intervention: Review of delivery intrathecal drug trial techniques (pump not implanted)
Anderson, Burchiel, and Cooke (2003)	Intervention: Trial of intrathecal injection vs. epidural infusion to determine candidacy for continuous intrathecal opioid therapy
Staats et al. (2004)	Population: Cancer-related pain in >85% of patients
Coffey et al. (2010)	Population: Duplicate (Coffey, 2009)
Corrado, Alperson, and Wright (2008)	Design: Retrospective cohort; pre-implantation pain scores based on recall
Doleys et al. (2006)	Design: Retrospective cohort with unclear selection process
Duarte, Raphael, Sparkes, et al. (2012)	Design: Retrospective cohort in which baseline data collected 4 years retrospectively based on recall, subjects not selected consecutively
Dunn et al. (2010)	Population: Patients taking oral opiates (presence of intrathecal delivery system unknown)
Ellis et al. (2008)	Population: >15% of patient population had cancer-related pain
Ilias et al. (2008)	Intervention: Patient-controlled analgesia device to be used with implanted intrathecal pumps
Maeyaert et al. (2003)	Intervention: Patient-controlled analgesia device to be used with implanted intrathecal pumps
Neuman, Eldrige, Qu, Freeman, and Hoelzer (2013)	Population: >15% of patient population had cancer-related pain
Paulozzi and Ryan (2006)	Population: Patients taking oral opiates (presence of intrathecal delivery system unknown)
Raffaeli et al. (2008)	Design: Retrospective study, participants not drawn consecutively or randomly, study was included in dossier, but not assessed by submitter
Raphael, Southall, Gnanadurai, Treharne, and Kitas (2002)	Design: Retrospective study, pre-treatment scores based on recall
Reig and Abejon (2009)	Population: >15% of patient population had cancer-related pain
Roberts, Finch, Goucke, and Price (2001)	Design: Retrospective study, pre-treatment scores based on recall
Saltari et al. (2007)	Population: Duplicate publication of a study included (Shaladi et al. 2007)
Siegler, Tuazon, Bradley O'Brien, and Paone (2014)	Design: Cross-sectional assessment of opiate overdose; does not include intrathecal delivery

Citation	Exclusion Criteria
Tutak and Doleys (1996)	Design: Retrospective study with unclear selection method and assessment of baseline pain scores
Wallace et al. (2010)	Treatment: Focuses on treatment effect of ziconotide in combination with other medications, not on intrathecal drug delivery systems, study was included in dossier but not assessed by submitter
Willis and Doleys (1999)	Design: Retrospective study with interviews to assess pain and function
Winkelmuller et al. (1999)	Design: Narrative review

Evidence Evaluation – Overall Strength of Body of Evidence by Outcome

Table 4 presents the submitter's assessment of the strength of evidence for the submitted outcomes, as well as the assessment of CEbP and rationale for this assessment.

Table 4. *Outcomes – Strength of Evidence*

Outcome	Strength of Evidence Assessment		Rationale
	Submitter	CEbP	
Level of pain (e.g., Global McGill, VASPI, Oswestry or Global pain indices)	High	Low	There is only one RCT which analyzes efficacy the treatment of chronic non-malignant pain. Most studies informing primary outcome measures of pain reduction are single-arm cohort studies that have poor internal and external validity. The body of evidence demonstrates improvements in pain, but there is a great deal of variation between studies with regard to populations, specific interventions, comparators, and outcomes. This heterogeneity does not allow for meta-analysis.
Quality of Life (e.g., CGI patient satisfaction scale, SF-36 quality of well-being, mood, activity level)	Moderate to High	Very low	Quality of life measures are reported inconsistently among cohort studies and different measures are used. The interventions are heterogeneous, as are the comparators. Quality of life improvements are reported, but the magnitude cannot be determined.
Level of disability (e.g., Oswestry disability, chronic illness problem inventory)	Moderate	Very low	Prospective and retrospective cohort studies inconsistently report on disability and use different outcome measures. Improvement is demonstrated in the several studies that measure disability, but the magnitude of benefit cannot be

Outcome	Strength of Evidence Assessment		Rationale
	Submitter	CEbP	
			determined. This finding is limited by heterogeneity in populations, specific interventions and comparators.
Pain-killer use (concomitant opioid or concurrent other painkillers)	Moderate	Very low	Several studies address the question of concomitant opiate use. Most report a reduction in systemic opioid use. However, results cannot be combined and should be interpreted with caution due to methodologic inconsistencies between studies.
Economic outcomes (e.g., cost-effectiveness/quality of life years, cumulative total cost, cost/period of time)	Moderate	Very low	There are several cost analyses and cost-utility analyses that rely on poor quality studies to inform the economic models. The efficacy and harms inputs are unreliable and thus the models themselves are not likely to be reliable.
Harms			
Mortality	Low	Very low	One poor quality retrospective cohort study used registry data to assess mortality one year post-implant.
Intrathecal granuloma	Low to Moderate	Very low	One poor quality retrospective cohort study reported on frequency of granuloma.
Infection	Moderate	Low	Multiple observational studies of fair to poor quality report site-related infections within a range of 2% to 9%.
Neurologic impairment due to inflammatory mass	Low	*None*	No included studies reported on neurologic impairment.
Cerebrospinal/dural fluid leak due to puncture, post dural puncture headache	Moderate to High	Low	Multiple fair and poor quality observation studies reported subdural headaches at a frequency of 3% to 15%.
Drug overdose/ toxicity due to component or system failure	Very low	Very low	One prospective cohort study reported drug toxicity due to a programming error.
Bleeding, wound dehiscence	Very low	Very low	One prospective cohort reported delayed wound healing.

Outcome	Strength of Evidence Assessment		Rationale
	Submitter	CEbP	
Tissue damage due to catheter migration	Moderate	Low	Multiple fair to poor quality observational studies report catheter migration.
Pocket seroma, hematoma, or migration	Moderate	Low	Several observational studies report seroma formation.
Reoperation or pump replacement due to pump or catheter failure	Moderate to High	Low	Multiple observational studies report reoperation with a variable incidence between studies.

Section 6: "The service must be cost-effective or cost neutral outside the investigational setting"
The submitter included three cost analyses (Bolash et al., 2015; Guillemette et al., 2013; Kumar et al., 2002), two cost-utility analyses comparing intrathecal drug devices to conventional pain treatments for chronic non-malignant pain (de Lissovoy et al., 1997; Kumar et al., 2013), and one cost-utility analysis (Dewilde et al., 2009) comparing intrathecal ziconotide to other pain therapies, including other intrathecal drug therapies. CEbP staff identified an additional cost analysis (Thrasher & Fisher, 2013) and a cost-utility analysis comparing intrathecal drug therapy to conventional pain treatment in chronic non-malignant pain (Biggs et al., 2011). Overall, the studies report that treatment of chronic non-malignant pain is costly and that intrathecal drug therapy is more expensive than conventional pain treatment, but also more effective. The incremental cost-effectiveness ratios (ICERs) are within accepted willingness to pay thresholds, which are traditionally cited between $50,000 to $100,000 U.S. dollars. The overall strength of the evidence is low, however, due to lack of internal and external validity of the published cost analyses. Table 5 summarizes findings and key limitations of the studies.

Table 5. Evidence Review- Economic Studies

Study Citation	Dossier QA	CEbP QA	Study Size (n)	Findings	Limitations / Comments
Bolash et al. (2015)	Good	Poor	n = 365	The average pump longevity was 5.4 (95% CI 5.0 to 5.8) years. The median system cost for implanted pumps was $10.46 per day, and for those pumps that reached the end of their battery life, the median cost was $9.26. The median cost was $44.59 for pumps that were explanted prematurely due	6% had cancer pain, 14% had spasticity. Data collected from retrospective review of 365 pts at the Cleveland Clinic. Costs of complications are not considered.

Study Citation	Dossier QA	CEbP QA	Study Size (n)	Findings	Limitations / Comments
				to lack of effectiveness or complications.	Medication costs also not considered.
Biggs et al. (2011)	Not included	Poor	n = 12	The mean costs of pain management prior to intrathecal pump implantation were £5,006 per year for 0.33 QALYs. If researchers included the waiting period for a pump, the average cost per year decreased to £4,086. The cost per year post-implantation was £13, 135 for 0.65 QALYs. The pump would be more cost-effective if the waiting period for the pump was not considered in the analysis, suggesting that there is a placebo effect related to being on a pump waiting list.	Small sample size, single center. No sensitivity analysis performed and costs not discounted. Incremental costs are not clear.
de Lissovoy et al. (1997)	Good	Fair	n = 1000 (simulation)	Cost effectiveness estimates ranged from $7,212 to $12, 276 per year of pain relief benefit of the intrathecal system.	This study was published in 1997, and therefore inputs informing analysis as well as monetary values are likely outdated. Alternative pain treatment extrapolated from case reports and expert opinion and may be overestimated. Good quality sensitivity analysis.
Dewilde et al. (2009)	Good	Fair	n = 3000 (simulated)	Intrathecal ziconotide compared to best supportive care has an incremental cost-effectiveness ratio of £ 27, 443 per quality-adjusted life year. Dosing of ziconotide was most likely to affect this ratio, and depending on the dose, the ICER ranged from £15, 500 to £44, 700.	In simulation, highest proportion of patients with malignant disease was 15%. The model was based on one RCT and values were also extrapolated from manufacturer data and expert

Study Citation	Dossier QA	CEbP QA	Study Size (n)	Findings	Limitations / Comments
					opinion. Harms of ziconotide are likely underestimated.
Guillemette et al. (2013)	Good	Fair	n = 555	There is an annual cost savings of $3111 (U.S. dollars) for intrathecal drug device compared to conventional pain therapy for non-cancer pain. The analysis was performed over a 30-year period and was based on comparison between claims data pre and post implant.	Comparator is pain pt prior to implementation, and pre-implantation costs may be overestimated. Cost analysis of claims data (outcomes not considered)
Kumar et al. (2002)	Good	Fair	n = 44	Over a 5-year period, the annual cost of intrathecal drug therapy is $5,882 compared to $7,600 for conventional pain therapy. Costs are in Canadian dollars. Costs are recovered at 28 months.	Outcomes and costs were based on a RCT in which pts received either intrathecal pain therapy or conventional pain therapy. The sensitivity analysis was not robust, and did not consider different estimates of conventional pain therapy costs.
Kumar et al. (2013)	Good	Poor	n = 169	In 2011 Canadian dollars, the cost of intrathecal drug therapy over a 10-year period is $61,442 compared to $48,408 for conventional pain management. The effectiveness per pt was higher in the intrathecal drug therapy group than in the conventional pain management group (2.4 vs 1.2), and the incremental cost effectiveness ratio is $11, 326 per quality-adjusted life year.	The model is based on a poor quality retrospective review in which the conventional pain management group is made up of pts who either failed or refused intrathecal therapy. The study is subject to selection bias that will have significant impact on the economic assumptions.
Thrasher	Not	Fair	n =	The mean medical costs for pain pts	This was a cohort study

Study Citation	Dossier QA	CEbP QA	Study Size (n)	Findings	Limitations / Comments
& FIsher (2013)	included		1,139	with intrathecal drug devices is high and variable. In 2011 U.S. dollars, mean costs were $15,900 per year pre-implant and $23,500 post-implant. There was a great deal of variability in cost results.	where costs were reported without a comparison group. From data provided, no conclusions can be made about reasons for high costs.

Section 7: Other payer coverage of the service

CEbP staff reviewed implantable infusion pump coverage policies for Aetna, Anthem, Cigna, and UnitedHealthCare and the Centers for Medicare and Medicaid Services. Across the national private payers reviewed, all cover the use of implantable infusion pumps for non-cancer pain for individuals who have been proven to be unresponsive to less invasive medical therapy. National Coverage Determination 280.14 and Local Coverage Determinations 33461, 35512, 33593, and 35134 also provide coverage of implantable infusion pumps for specific individuals. Common medical necessity criteria across payers include:

- Non-adequate response to non-invasive methods of pain control (e.g., systemic opioids, surgical, psychologic or physical treatment modalities) – *some payers define this as a minimum trial of six months*
- Further surgical intervention is not indicated
- Psychological evaluation documents that pain is not psychological in origin and individual would benefit from implantation with an infusion pump
- Attempts have been made to eliminate physical and behavioral contributors to exaggerated sense of pain
- No contraindications to implantation exist (e.g., sepsis)

Some payers require a preliminary trial of intraspinal opioid drug administration with a temporary intrathecal/epidural catheter to establish adequate acceptable pain relief (defined as a 50% reduction in pain), degree of side effects including the impact on activities of daily living, and patient acceptance. In addition, the NCD 280.14 stipulates that individuals must have a life expectancy of at least three months to be eligible for an implantable infusion pump for severe, chronic, intractable non-cancer pain.

Payers also stipulate contraindications to implantable infusion pumps including:

- Individuals with an active infection that may increase the risk of an implantable infusion pump
- Individuals whose body size is insufficient to support the weight and bulk of the device

- Individuals with a known allergy or hypersensitivity to the drug being administered
- Individuals with other implanted programmable devices where crosstalk between devices may inadvertently change the prescription (Aetna, 2015; Anthem, 2015; Cigna, 2015; UnitedHealthCare, 2015)

Summary

There is a fairly consistent body of poor quality evidence drawn mostly from fair to poor quality observational studies demonstrating short- and long-term clinically significant (greater than or equal to 30%) reductions in pain in patients with chronic non-cancer pain treatment with intrathecal drug therapy. Additional studies report improvement in quality of life and functional capabilities, but this is done inconsistently and magnitude of benefit cannot be determined. Common device-related complications include pump failure, reoperation due to pump or catheter failure, and headache. Infection, seroma, granuloma, and catheter migration are reported less frequently. There are no long-term RCTs comparing intrathecal drug therapy to conventional pain therapy. Studies are variable in population, intrathecal medications, and length of follow-up, and due to this heterogeneity, the overall strength and consistency of either benefits or harms cannot be estimated.

Findings are limited to populations of individuals with severe chronic pain that has failed multiple alternative therapies. It is impossible to conclude what groups within this population would most benefit from or be harmed by intrathecal drug therapy from this evidence. The cost of intrathecal drug therapy is higher than conventional pain therapy in the short-term. However, long-term savings is estimated by modeling studies with particular assumptions. Cost-utility analyses report incremental cost-effectiveness ratios within well-accepted willingness to pay thresholds, however assumptions are based on poor quality evidence.

There are several common biases present in the majority of studies that limit findings further including author affiliation or funding from the device manufacturer, a non-comparative design that limits internal validity, and small populations drawn from single centers which limits external validity.

Several national private payers cover the use of implantable infusion pumps for non-cancer pain for individuals who have been proven to be unresponsive to less invasive medical therapy and meet certain clinical criteria.

Appendix A. Search Strategy

The *MEDLINE®* Search Strategy was adapted from the Washington Health Technology Report (Turner et al., 2007) and studies published after the search dates from the Turner et al (2007) were included to update the existing systematic review.

MEDLINE® Search

Database: Ovid MEDLINE(R) and Ovid OLDMEDLINE(R) 1946 to Week 2 October 2015 Search Strategy:

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1 exp drug delivery system/ or (Drug delivery systems or Infusion pump or Infusion pumps, implantable or catheters indwelling or indwelling catheter).de.

2 ((Intrathecal drug administration or injections spinal or injection, intraspinal).de. or Intrathecal.mp. or intraspinal.mp. or epidural.mp. or subarachnoid.mp. or implant$.mp.) and (pump$ or port$ or continuous).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

3 1 or2

4 limit 3 to (english language and humans and yr="2008 -Current")

5 (exp pain/ or pain$.ti,ab.) and (chronic or intractable or refractory or persistent).ti,ab.

6 Pain intractable.de.

7 (soft tissue or (pancreatitis and chronic) or arteriosclerosis obliterans or fibromyalgia or fibrositis or arthrit$ or back or neck or tmj or MS or phantom or allodynia or sciatica or neuralgia or neuropath$).ti,ab. or neck pain.de.

8 exp musculoskeletal diseases/ or exp musculoskeletal disease/ or exp joint diseases/ or exp arthropathy/ or exp back pain/ or exp backache/ or exp multiple sclerosis/

9 exp analgesics, opioid/ or exp narcotics/ or exp narcotic analgesic agent/ or exp opiates/

10 (Actiq or Avinza or Combunox or Depodur or Dolophine or Duragesic or Duramorph or Fentanyl or Fentora or Infumorph or Ionsys or Kadian or Methadone or Methadose or Morphine or MS contin or Nasalfent or Numorphan or Opana or Oxycodone or Oxycontin or Oxymorphone or Percocet or Percodan or Sufenta or Sufentanil or Tramadol or Ultram).mp.

11 (Ziconotide or baclofen).mp.

12 5 or 6 or 7 or 8 or 9 or 10 or 11

13 4 and 12

14 13 not ((letter or editorial or news or comment or note or conference paper).de. or (letter or editorial or news or comment).pt.)

15 14 not (exp neoplasm/ or exp neoplasms/ or Cancer.mp. or Carcinoma.mp. or Childbirth.mp. or intrapartum.mp. or Labor.mp. or Labour.mp. or perinatal.mp. or postpartum.mp. or Postop.mp. or Post operative.mp. or Post-op.mp. or Post-operative.mp.)

16 remove duplicates from 15

The search terms, “intrathecal pump,” “intraspinal pump”, “infusion pump”, “implantable pump”, and “pain” were used in the remaining core source searches, which included: Hayes, Inc., the National Institute for Health and Care Excellence (NICE), Cochrane Library, PubMed Health, the Blue Cross/Blue Shield Health Technology Assessment (HTA) program, the Veterans Administration Technology Assessment Program (VATAP), *BMJ Clinical Evidence*, the Washington State Health Technology Assessment Program, the Agency for Healthcare Research and Quality (AHRQ), and Tufts Cost-Effectiveness Analysis Registry. Systematic reviews that were performed in the last ten years were included. Archived government reports were not included.

Appendix B. MEDLINE Results

Table 1. *MEDLINE Articles Selected for Full Text Review*

Citation	Included?	Comments/Rationale
Biggs et al. (2011)	Yes	Cost-analysis
Borrini et al. (2014)	No	Study included adults with intrathecal catheter placement for baclofen administration to treat spasticity
T. R. Deer et al. (2010)	No	Consensus guidelines without systematic review
Duse et al. (2009)	Yes	Prospective cohort
Godsi, Saadatniaki, Aghdashi, Firoozabadi, and Dadkhah (2010)	No	Retrospective study that relies on recall for pain improvement
Grider et al. (2011)	Yes	Retrospective cohort
Kim et al. (2011)	Yes	Retrospective cohort
Kongkam et al. (2009)	Yes	Retrospective cohort
Lara et al. (2011)	Yes	Prospective cohort
Lee et al. (2013)	No	Addresses treatment of post-operative pain
Mohammed et al. (2013)	No	Study length: 6 hours
Perruchoud et al. (2011)	No	Study comparing different flow rates of intrathecal medications
Prager et al. (2014)	No	Narrative review
R. Rauck, Coffey, et al. (2013)	Yes	Randomized controlled trial with study duration of 22 days; included for harms only
R. Rauck, Deer, et al. (2013)	Yes	Prospective cohort
Rosen et al. (2013)	No	Intervention: Drug-drug comparison (intrathecal Infumorph to compounded morphine)
Schechtmann, Lind, Winter, Meyerson, and Linderoth (2010)	No	Intrathecal pump implanted on 4 patients only
Seemann et al. (2012)	No	Intervention comparing intrathecal fentanyl to sufentanil; retrospective study with exclusion criteria that are likely to create selection bias
Thrasher and Fisher (2013)	Yes	Cost analysis
Tomycz, Ortiz, McFadden, Urgo, and Moossy (2012)	No	Addresses management of an intrathecal catheter associated-complication
Tomycz, Ortiz, and Moossy (2010)	No	Retrospective cohort that relies on recall for pain improvement
Varhabhatla and Zuo (2012)	No	Addresses complication of intrathecal catheter placement used to treat spasticity with baclofen in a pediatric population

Appendix C. Quality Assessment Forms

Table 1a. *Systematic Reviews Quality Assessment*

Risk of Bias Assessment Criteria	T. R. Deer, Levy, et al. (2012)		T. R. Deer, Prager, Levy, et al. (2012b)		T. R. Deer, Prager, Levy, et al. (2012a)		(Duarte, Raphael, Southall, et al., 2012)	
	Submitter	CEbP	Submitter	CEbP	Submitter	CEbP	Submitter	CEbP
1.1 The study addresses an appropriate and clearly focused question.	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
1.2 An adequate description of the methodology used is included, and the methods used are appropriate to the question.	Yes	No	Yes	No	Yes	No	Yes	Yes
1.3 The literature search is sufficiently rigorous to identify all the relevant studies.	Yes	Unclear	Yes	Unclear	Yes	Unclear	Yes	Yes
1.4 The criteria used to select articles for inclusion is appropriate.	Yes	Unclear	Yes	Unclear	Yes	Unclear	Yes	Yes
1.5 Study quality is assessed and taken into account.	Yes	No	Yes	No	Yes	No	Yes	Yes
1.6 There are enough similarities between the studies selected to make combining them reasonable.	Yes	No	Yes	No	Yes	Unclear	Yes	No
1.7 There is a conflict of interest statement.	Yes	Yes. Multiple authors consult for pharma, including Medtronic	Yes	Yes. Multiple authors consult for pharma, including Medtronic	Yes	Yes. Multiple authors consult for pharma, including Medtronic	Yes	Yes
1.8 There is a description of the source(s) of funding.	They have not influenced	Funded by Medtronic and Azure Pharma	They have not influenced	Funded by Medtronic and Azure Pharma	Yes, they have not be influenced	Funded by Medtronic and Azur Pharma	Unclear	Yes
2.1 How well was the study done to minimize bias?	**Good**	**Poor**	**Good**	**Poor**	**Good**	**Poor**	**Good**	**Fair**
2.2 Are the results of this study directly applicable to the patient group targeted by this key question?	Yes	Yes	Yes	Yes	Yes	Yes, for harms	Yes	Yes
2.3 Comments	None	None	None	No	None	None	None	None

Table 1b. *Systematic Reviews Quality Assessment*

Risk of Bias Assessment Criteria	Falco et al. (2013)		Hayek, Deer, et al. (2011)		Hayes (2014)		Narouze et al. (2014)	
	Submitter	CEbP	Submitter	CEbP	Submitter	CEbP	Submitter	CEbP
1.1 The study addresses an appropriate and clearly focused question.	Yes	Yes	*Not included in dossier submission*	Yes	*Not included in dossier submission*	Yes	Yes	Yes
1.2 An adequate description of the methodology used is included, and the methods used are appropriate to the question.	Yes	Yes		Yes		Yes	Yes	Yes
1.3 The literature search is sufficiently rigorous to identify all the relevant studies.	Yes	Unclear, detailed search strategy not included		Unclear, detailed search strategy not included		Unclear, detailed search strategy not included	Yes	Unclear
1.4 The criteria used to select articles for inclusion is appropriate.	Yes	Yes		Yes		Yes	Yes	No Concern for selection bias as criteria are based on particular hypothesis.
1.5 Study quality is assessed and taken into account.	Yes	Yes		Yes		Yes	Yes	No
1.6 There are enough similarities between the studies selected to make combining them reasonable.	Yes	n/a (did not combine)		No, studies are not combined		No, studies are not combined	Yes	Unclear
1.7 There is a conflict of interest statement.	Yes	Yes		No, Hayes in an independent body		No, Hayes in an independent body	Unclear	No
1.8 There is a description of the source(s) of funding.	Yes, they have not influenced	Yes, no external funding		n/a		n/a	Unclear	No
2.1 How well was the study done to minimize bias?	**Good**	**Fair**		**Good**		**Good**	**Fair**	**Poor**
2.2 Are the results of this study directly	Yes	Yes		Yes		Yes	Somewhat	Yes

Risk of Bias Assessment Criteria	Falco et al. (2013)		Hayek, Deer, et al. (2011)		Hayes (2014)		Narouze et al. (2014)	
	Submitter	CEbP	Submitter	CEbP	Submitter	CEbP	Submitter	CEbP
applicable to the patient group targeted by this key question?								
2.3 Comments	None	None		None		None	Includes all types of intrathecal drug treatments and most are not high quality studies. They state this study should be repeated.	None

Table 1c. *Systematic Reviews Quality Assessment*

Risk of Bias Assessment Criteria	Noble et al. (2008)		Noble et al. (2010)		Patel et al. (2009)		Turner et al. (2007)	
	Submitter	CEbP	Submitter	CEbP	Submitter	CEbP	Submitter	CEbP
1.1 The study addresses an appropriate and clearly focused question.	*Not included in dossier submission*	Yes	Yes	Yes	Yes	Yes	Yes	Yes
1.2 An adequate description of the methodology used is included, and the methods used are appropriate to the question.		Yes	Yes	Yes	Yes	Yes	Yes	Yes
1.3 The literature search is sufficiently rigorous to identify all the relevant studies.		Yes	Yes	Yes	Yes	Unclear	Yes	Unclear
1.4 The criteria used to select articles for inclusion is appropriate.		Yes, inclusion criteria determined a	Yes	Yes	Yes	Yes	Yes	Yes

Risk of Bias Assessment Criteria	Noble et al. (2008)		Noble et al. (2010)		Patel et al. (2009)		Turner et al. (2007)	
	Submitter	CEbP	Submitter	CEbP	Submitter	CEbP	Submitter	CEbP
		prior to reduce bias						
1.5 Study quality is assessed and taken into account.		Yes	Yes	Yes	Yes	Yes	Yes	Yes
1.6 There are enough similarities between the studies selected to make combining them reasonable.		No, substantial heterogeneity of data	Yes	No, heterogeneity of data	Yes	Yes	Yes	No, heterogeneity
1.7 There is a conflict of interest statement.		No, but prepared by ECRI institute, an independent body	Yes	No	Yes	Yes, many authors are medical directors of pain centers and one author receives funding from Medtronic	Yes	Yes, one author is affiliated with Medtronic
1.8 There is a description of the source(s) of funding.		Yes, Washington State	Yes, they have not influenced	No	Yes, they have not influenced	No	Unclear	Yes, supported by the Medical Aid Fund of the Washington State Department of Labor and Industries
2.1 How well was the study done to minimize bias?		**Good**	**Good**	**Good**	**Good**	**Fair**	**Good**	**Good**
2.2 Are the results of this study directly applicable to the patient group targeted by this key question?		Yes	Yes	Yes	Yes	Yes	Yes	Yes
2.3 Comments		Outdated	Noble employed by ECRI. Their assessment of intrathecal studies included	None	None	Low quality evidence with strong recommendation for intrathecal	Includes some small studies and studies with off label usage.	None

Risk of Bias Assessment Criteria	Noble et al. (2008)		Noble et al. (2010)		Patel et al. (2009)		Turner et al. (2007)	
	Submitter	CEbP	Submitter	CEbP	Submitter	CEbP	Submitter	CEbP
			small studies of less than n=20 and substantial off label usage (e.g. Angel 1998 with n=11; Hassenbusch 1995 n=18 and most with off label use; Kumar 2001 n=16 with some off label; Mironer 2001 n=24 most with off label usage; Pimenta 1998 n=11, off-label; and Rainov 2001 n=27, off-label usage)			infusion pump	Although focus is on SynchroMed, search criteria do not limit to only SynchroMed infusion systems.	

Table 2. *Randomized Controlled Trials Quality Assessment*

Risk of Bias Assessment Criteria	Raphael et al. (2013)		Rauck et al. (2006)		Rauck, et al. (2013)		Wallace et al. (2006)	
	Submitter	CEbP	Submitter	CEbP	Submitter	CEbP	Submitter	CEbP
1.1 An appropriate method of randomization was used to allocate participants to intervention groups.	Yes	Yes	Yes	Unclear	*Not included in dossier submission*	Yes	Yes	Unclear, method of randomization not described
1.2 An adequate concealment method was used such that investigators, clinicians, and participants could not influence enrolment or intervention allocation.	Yes	Yes	Yes	Unclear		Yes	Yes	Unclear, method of blinding not described
1.3 The intervention and control groups are similar at the start of the trial (The only difference between groups is the treatment under investigation).	Yes	Yes	Yes	Unclear, demographic and pain diagnosis are similar, however types and dosages of oral medications among groups vary		Yes	Yes	Unclear, the mean opioid use is much higher for the placebo group (unadj significance was not reported and it is not clear if adj was appropriate
1.4 Investigators, participants, and clinicians were kept "blind" about treatment allocation and other important confounding/prognostic factors. If the answer is no, describe any bias that might have occurred.	Yes	Yes	Yes	Unclear		Yes	Yes	Unclear
1.5 The intervention and control groups received the same care apart from the interventions studied.	Yes	Yes	Yes	Yes		Yes	Yes	Yes
1.6 The study had an appropriate length of follow-up.	Yes	Yes	Yes	No, 3 weeks		No, 22 days	No	No, 6 days
1.7 All groups were followed up for an equal length of time (or the analysis was adjusted to allow for differences in length of follow-up.)	Yes	Yes	Yes	Yes		Yes	Study titration of ziconotide (6 days) and then primary endpoints, followed for add'l 5-6 days on maintenance prior to study termination	Yes
1.8 What percentage of the	70%	66%	Dropout rate	9/112 (8%) in tx		2.9%	N=1 (0.4% of total	3% in each group

Risk of Bias Assessment Criteria	Raphael et al. (2013)		Rauck et al. (2006)		Rauck, et al. (2013)		Wallace et al. (2006)	
	Submitter	CEbP	Submitter	CEbP	Submitter	CEbP	Submitter	CEbP
individuals or clusters recruited into each group of the study dropped out before the study was completed? What percentage did not complete the interventions?			due to AEs was comparable: ziconotide (n=6, 5.4%) and placebo groups (n=5, 4.6%; P=0.80). N=3 in each group discontinued trt for other reasons.	group; 8/108 (7.4%) in placebo group			study population), randomized to ziconotide and discontinued due to catheter dislodgement, after a new catheter implanted was randomized to placebo, this pt was excluded from the ITT population in order to avoid double counting but was included in the ziconotide group for safety analyses, n=54 ziconotide and n=11 placebo were continued on in maintenance (responders)	
1.9 All the subjects were analyzed in the groups to which they were randomly allocated (intention to treat analysis).	Yes	Yes	Yes	ITT used for safety measures and primary and secondary pain score measures. However, last observation carried forward method was used for missing data. Per protocol used of other measures		Yes, for the 3 subjects with missing data, however missing data otherwise was carried forward using average pain score from week prior	At the end of titration phase, non-responders were crossed over to the placebo arm	Modified intention to treat, data analyzed for all participants who had at least one f/u pain score, missing values were left missing
1.10 All relevant outcomes are measured in a standard, valid, and reliable way.	Yes	Yes	Yes	Yes		Yes	Yes	Yes
1.11 The study reported on only surrogate outcomes. (If so, comment	No	No	No	No		No	No	No

Risk of Bias Assessment Criteria	Raphael et al. (2013)		Rauck et al. (2006)		Rauck, et al. (2013)		Wallace et al. (2006)	
	Submitter	CEbP	Submitter	CEbP	Submitter	CEbP	Submitter	CEbP
on the strength of evidence associated the surrogate with the important clinical outcome for this topic).								
1.12 The study uses a composite outcome as the primary outcome. If so, comment on the appropriateness of the composite and whether any single outcome strongly influenced the composite.	No	No	No	No		No	No	No
1.13 Competing interests of members have been recorded and addressed.	Yes, all are outlined clearly	Yes	Noted but not discussed	No		Yes, multiple authors employed by or received fees from Medtronic, Inc	Yes	Yes, multiple study authors employed by Elan Pharmaceuticals
1.14 View of the funding body have not influenced the content of the study.	No, they have not influenced	Yes	They have not influenced	Yes. Funded by Elan Pharmaceuticals (makers of Ziconotide)		No, study supported by Medtronic	They have not influenced	Funded by Elan Pharmaceuticals (makers of Ziconotide)
2.1 How well was the study done to minimize bias?	**Good**	**Good**	**Good**	**Fair**		**Fair**	**Good**	**Poor**
2.2 Are the results of this study directly applicable to the patient group targeted by this topic?	Yes	Yes	Yes	Not for effectiveness given short follow-up duration		No for effectiveness given study duration	---	No, short f/u duration
2.3 Comments	Trial was halted due to excessive drop out from the dose reduction treatment arm.	70% of participants in intervention group (dose reduction) dropped out due to increased pain.	None	Funding and lack of detailed reporting on allocation, randomization, and blinding raises concern for bias. 3 week follow-up is not sufficient to determine long-		Only harms included, study length 22 days	---	6 day f/u in inpatient hospital setting, caution must be used in interpreting effects given study duration

Risk of Bias Assessment Criteria	Raphael et al. (2013)		Rauck et al. (2006)		Rauck, et al. (2013)		Wallace et al. (2006)	
	Submitter	CEbP	Submitter	CEbP	Submitter	CEbP	Submitter	CEbP
		Last observed outcome used due to high drop-out rate		term benefits and harms of device				

Table 3a. *Prospective Cohort Study Quality Appraisal*

	Anderson and Burchiel (1999)		Deer et al. (2004)		Duse et al. (2009)		Hamza et al. (2012)	
Risk of Bias Assessment Criteria	Submitter	CEbP	Submitter	CEbP	Submitter	CEbP	Submitter	CEbP
1.1 The study addresses an appropriate and clearly focused question.	Yes	Yes	Yes	No	*Not included in dossier submission*	Yes	Yes	Yes
1.2 The two groups being studied are selected from source populations that are comparable in all respects other than the factor under investigation.	One group, no control	n/a	No, one group	n/a		n/a	One group, no control	n/a
1.3 The study indicated how many of the people asked to take part did so, in each of the groups being studied.	Yes	No, did not explicitly state how many asked	Yes	Yes, 136/154 (88%) pts who had a successful trial were implanted with IDDS		No, however authors recorded reason why pts trialed did not receive a pump (30/42) went on to have pump implanted	Yes	No
1.4 The likelihood that some eligible subjects might have the outcome at the time of enrollment is assessed and taken into account in the analysis.	n/a	Yes, baseline pain score assessed	n/a	Yes, baseline pain assessed		n/a	Yes	Yes
1.5 What percentage of individuals recruited into each arm of the study dropped out before the study was completed?	33%	33%, reason for drop-out include: death (10%), inadequate pain relief (3%), drug-seeking behavior (3%), and incomplete f/u data (17%)	Unclear, assume they adjust registry with the number of pts in the study diminishing from 0 to 6 to 12 months, it was only noted as missing data	47% of those who had device implanted did not have complete f/u		Unclear	None	Unclear
1.6 Comparison is made between full participants and those who dropped out or were lost to follow up, by exposure status.	Yes	Yes	Yes	No, however a comparison is made between those who had a successful trial and did not receive IIDS and those who completed the full study		No	n/a	No

Risk of Bias Assessment Criteria	Anderson and Burchiel (1999)		Deer et al. (2004)		Duse et al. (2009)		Hamza et al. (2012)	
	Submitter	CEbP	Submitter	CEbP	Submitter	CEbP	Submitter	CEbP
1.7 The study employed a precise definition of outcome(s) appropriate to the key question(s).	Yes	Yes	Yes	Yes		Yes	Yes	Yes
1.8 The assessment of outcome(s) is made blind to the exposure status.	No	No	Unclear	No		No	Unclear	No
1.9 Where outcome assessment blinding was not possible, there is some recognition that knowledge of exposure status could have influenced the assessment outcome.	Unclear	No	Yes	No		No	No	No
1.10 The measure of assessment of exposure is reliable.	Yes	Yes	Yes	Yes		Yes	Yes	Yes
1.11 Exposure level or prognostic factor is assessed more than once.	Yes	n/a	Yes	n/a		n/a	Yes	n/a
1.12 Evidence from other sources is used to demonstrate that the method of outcome assessment is valid and reliable.	Yes	Yes	Yes	Yes		Yes	Yes	Yes
1.13 The study had an appropriate length of follow-up.	Yes	Yes	Yes	Yes, 12 months		Yes	Yes	Yes, 36 months
1.14 All groups were followed for an equal length of time (or analysis was adjusted to allow for differences in length of follow-up).	Yes	Yes	Yes	Yes		Yes, 24 months	Yes	Yes
1.15 The main potential confounders are identified and taken into account in the design and analysis	Unclear	No	Unclear	Unclear		Unclear	Yes	Yes
1.16 Have confidence intervals been provided?	Yes	Yes	Yes	No		No	Yes	Yes
1.17 Competing interests of members have been recorded and addressed.	Yes	No	Unclear	No		Yes	Unclear	No
1.18 Views of funding body have not influenced the content of the study.	Unclear	Unclear, funded by Medtronic	Unclear	Unclear		Unclear	Unclear	Unclear
2.1 How well was the study done to minimize the risk of bias or confounding, and to establish a causal relationship between exposure and effect?	**Good**	**Poor**	**Fair**	**Poor**		**Poor**	**Good**	**Poor**
2.2 Are the results of this study directly applicable to the patient group targeted by this topic?	Yes	Yes	Yes	Yes		Yes	Yes	Yes
2.3 Taking into account clinical	Yes	No	Yes	No		No	Yes	No

Risk of Bias Assessment Criteria	Anderson and Burchiel (1999)		Deer et al. (2004)		Duse et al. (2009)		Hamza et al. (2012)	
	Submitter	CEbP	Submitter	CEbP	Submitter	CEbP	Submitter	CEbP
considerations, your evaluation of the methodology used, and the statistical power of the study, are you certain that the overall effect is due to the exposure being investigated?								
2.4 Comments	---	Prospective cohort with no control, 33% lost to f/u and analyzed per protocol, potential confounding factors not considered in analysis, single-center location, limits generalizability	Registry, internal control is baseline readings, placebo effect no assessable so could be biased towards improvement, errors not shown (although must have been calculated to do the statistical analysis)	Large loss to f/u and analysis of results was per protocol, adverse events were only measured in those who completed the study, and difference in pain ratings were only assessed in those who did not receive IDDS and those who completed the study, results are likely biased in favor of IDDS		29% of those who underwent a trial of interthecal opiate did not qualify for pump implantation, no f/u assessment of those pts, it is unclear if all 30 implanted pts completed the 2 year study period	---	Single cohort, # recruited and # completing study are not specified, risk of bias in favor of intervention is high

Table 3b. *Prospective Cohort Study Quality Appraisal*

Risk of Bias Assessment Criteria	Lara et al. (2011)		Rauck, Deer, et al.(2013)		Shaladi et al. (2007)		Thimineur et al. (2004)	
	Submitter	CEbP	Submitter	CEbP	Submitter	CEbP	Submitter	CEbP
1.1 The study addresses an appropriate and clearly focused question.	*Not included in dossier submission*	Yes	*Not included in dossier submission*	Yes	Yes	Yes	Yes	Yes
1.2 The two groups being studied are selected from source populations that are comparable in all respects other than the factor under investigation.		n/a		n/a	n/a	n/a	Yes	No, the control either did not tolerate trial of intrathecal medication or declined implantation, there is an additional group which

Risk of Bias Assessment Criteria	Lara et al. (2011)		Rauck, Deer, et al.(2013)		Shaladi et al. (2007)		Thimineur et al. (2004)	
	Submitter	CEbP	Submitter	CEbP	Submitter	CEbP	Submitter	CEbP
								differed from the intervention group only that they enrolled later
1.3 The study indicated how many of the people asked to take part did so, in each of the groups being studied.		No		No	Yes	No	No	No
1.4 The likelihood that some eligible subjects might have the outcome at the time of enrollment is assessed and taken into account in the analysis.		n/a		n/a	n/a	Yes	Yes	Yes
1.5 What percentage of individuals recruited into each arm of the study dropped out before the study was completed?		0		45%, reasons for withdrawal included withdrawn consent, lack of pain relief, death not related to device, non-device related adverse events, and device-related adverse events	0	Unclear	19/28	25.2%
1.6 Comparison is made between full participants and those who dropped out or were lost to follow up, by exposure status.		n/a		No	n/a	No	Yes	No
1.7 The study employed a precise definition of outcome(s) appropriate to the key question(s).		Yes		Yes	Yes	Yes	Yes	Yes
1.8 The assessment of outcome(s) is made blind to the exposure status.		No		No	Unclear	No	Unclear	No
1.9 Where outcome assessment blinding was not possible, there is some recognition that knowledge of exposure status could have Yes influenced the assessment outcome.		No		No	Yes	No	No	No
1.10 The measure of assessment of		Yes		No	Yes	Yes	Yes	Yes

Risk of Bias Assessment Criteria	Lara et al. (2011)		Rauck, Deer, et al.(2013)		Shaladi et al. (2007)		Thimineur et al. (2004)	
	Submitter	CEbP	Submitter	CEbP	Submitter	CEbP	Submitter	CEbP
exposure is reliable.								
1.11 Exposure level or prognostic factor is assessed more than once.		n/a		n/a	Yes	n/a	Yes	n/a
1.12 Evidence from other sources is used to demonstrate that the method of outcome assessment is valid and reliable.		Yes		Yes	Yes	Yes	Yes	Yes
1.13 The study had an appropriate length of follow-up.		Yes, 24 months		Yes, 12 months	Yes	Yes, 12 months	Yes	Yes, 36 months
1.14 All groups were followed for an equal length of time (or analysis was adjusted to allow for differences in length of follow-up).		Unclear		Yes	Yes	n/a	Yes	Yes
1.15 The main potential confounders are identified and taken into account in the design and analysis		Unclear		Unclear	Yes	No	Unclear	Unclear
1.16 Have confidence intervals been provided?		No		No	Yes	No	Yes	Yes
1.17 Competing interests of members have been recorded and addressed.		Yes		Recorded but not addressed, multiple authors receive compensation from Flowonix	Yes	No	Yes	No
1.18 Views of funding body have not influenced the content of the study.		Unclear		No, funded by Flowonix	Unclear	Unclear	Unclear	No, pharma funded
2.1 How well was the study done to minimize the risk of bias or confounding, and to establish a causal relationship between exposure and effect?		**Fair**		**Poor**	**Good**	**Poor**	**Fair**	**Fair**
2.2 Are the results of this study directly applicable to the patient group targeted by this topic?		Yes		Yes	Yes	Yes	Yes	Yes
2.3 Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, are you certain that the overall effect is due to the exposure being investigated?		Yes		No	Yes	No	Yes	No, not entirely
2.4 Comments		All pts had		3% of	---	The number of pts	Since it was not	Having a

Risk of Bias Assessment Criteria	Lara et al. (2011)		Rauck, Deer, et al.(2013)		Shaladi et al. (2007)		Thimineur et al. (2004)	
	Submitter	CEbP	Submitter	CEbP	Submitter	CEbP	Submitter	CEbP
		failed back surgery syndrome, it is unclear what percent had a successful intrathecal trial, no mention is made of missing values (if any) and how they may have been addressed		participants had cancer pain, only 55% of participants completed study at 6 months, and analysis was per protocol, placing study at high risk of bias in favor of intervention		recruited and who were lost to f/u was not stated, study included pts with vertebral fracture refractory to other treatments for 1-3 months and lasted 12 months, without a comparison group, it is unclear if results are due to the natural improvement in vertebral fracture pain or to intrathecal morphine	blinded, this could influence it in either direction, graded as fair because small study and most PR were receiving more than just morphine (so off label)	comparison group who declined or failed intrathecal therapy is a relative strength of the study, a major weakness is that pts lost to f/u were not analyzed

Table 3c. *Prospective Cohort Study Quality Appraisal*

Risk of Bias Assessment Criteria	Wallace et al. (2008)		Wesemann et al. (2014)	
	Submitter	CEbP	Submitter	CEbP
1.1 The study addresses an appropriate and clearly focused question.	Yes	Yes	Yes	Yes
1.2 The two groups being studied are selected from source populations that are comparable in all respects other than the factor under investigation.	One group, no control	n/a, one cohort	One group, no control	n/a
1.3 The study indicated how many of the people asked to take part did so, in each of the groups being studied.	Yes	No	Yes	No
1.4 The likelihood that some eligible subjects might have the outcome at the time of enrollment is assessed and taken into account in the analysis.	Unclear	Yes	n/a	Unclear
1.5 What percentage of individuals recruited into each arm of the study dropped out before the study was completed?	89%	Unclear, 81.5 % received ziconotide for less than one year	15%	15%
1.6 Comparison is made between full participants and those who dropped out or were lost to follow up, by exposure status.	Yes	No	Yes	No
1.7 The study employed a precise definition of outcome(s) appropriate to the key question(s).	Yes	Yes	Yes	Yes

Risk of Bias Assessment Criteria	Wallace et al. (2008)		Wesemann et al. (2014)	
	Submitter	CEbP	Submitter	CEbP
1.8 The assessment of outcome(s) is made blind to the exposure status.	No	No	No	No
1.9 Where outcome assessment blinding was not possible, there is some recognition that knowledge of exposure status could have influenced the assessment outcome.	No	No	No	No
1.10 The measure of assessment of exposure is reliable.	Yes	Yes	Yes	Yes
1.11 Exposure level or prognostic factor is assessed more than once.	Yes	n/a	Yes	n/a
1.12 Evidence from other sources is used to demonstrate that the method of outcome assessment is valid and reliable.	Yes	Yes	Yes	n/a, outcomes are harms and flow rate accuracy
1.13 The study had an appropriate length of follow-up.	Yes	No, pain outcomes data analyzed at two months	Yes	Yes, 12 months
1.14 All groups were followed for an equal length of time (or analysis was adjusted to allow for differences in length of follow-up).	Yes	n/a	Yes	Yes
1.15 The main potential confounders are identified and taken into account in the design and analysis	Unclear	Unclear	Yes	Unclear
1.16 Have confidence intervals been provided?	Yes	No	Yes	Yes
1.17 Competing interests of members have been recorded and addressed.	Yes	Yes, recorded, multiple authors are affiliated with pharmaceutical industry, include Elan Pharmaceuticals	Yes	Yes, most authors work for Medtronic
1.18 Views of funding body have not influenced the content of the study.	Unclear	No, funded by Elan Pharmaceuticals	Unclear	No, funded by Medtronic
2.1 How well was the study done to minimize the risk of bias or confounding, and to establish a causal relationship between exposure and effect?	**Good**	**Poor**	**Good**	**Poor**
2.2 Are the results of this study directly applicable to the patient group targeted by this topic?	Yes	Yes	Yes	Yes
2.3 Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, are you certain that the overall effect is due to the exposure being investigated?	Yes	No	Yes	No
2.4 Comments	The focus of this study was on the safety and tolerability of ziconotide	2.5% of pts had pain secondary to cancer, main objective was to study safety and tolerability of drug rather than efficacy	---	54% of pts were being treated for spasticity without pain, study too small to detect all possible harms, frequencies of harms is low compared to other studies, concern for bias given lack of blinding of investigators and affiliated with Medtronic

Table 4a. *Retrospective Cohort Study Quality Appraisal*

Risk of Bias Assessment Criteria	Alti et al. (2010)		Coffey et al. (2009)		Grider et al. (2011)		Hayek, Veizi, et al. (2011)	
	Submitter	CEbP	Submitter	CEbP	Submitter	CEbP	Submitter	CEbP
1.1 The study addresses an appropriate and clearly focused question.	*Not included in dossier submission*	Yes	[*classified as case series*]	Yes	*Not included in dossier submission*	Yes	Yes	Yes
1.2 The two groups being studied are selected from source populations that are comparable in all respects other than the factor under investigation.		n/a		Unclear		n/a	One group, no control	Yes
1.3 The study indicated how many of the people asked to take part did so, in each of the groups being studied.		n/a		Registries about 90% complete		Yes	Yes	Yes
1.4 The likelihood that some eligible subjects might have the outcome at the time of enrollment is assessed and taken into account in the analysis.		Yes		n/a		Yes	Yes	n/a
1.5 What percentage of individuals recruited into each arm of the study dropped out before the study was completed?		24.6% of pts were included due to cancer diagnosis, complications of pump, and emigration; unclear percentage of pts with missing data		n/a		9% did not tolerate trial and did not have IDDS implanted	15%	0% , chart review
1.6 Comparison is made between full participants and those who dropped out or were lost to follow up, by exposure status.		No		n/a		No	Yes	n/a
1.7 The study employed a precise definition of outcome(s) appropriate to the key question(s).		Yes		Yes		Yes	Yes	Yes
1.8 The assessment of outcome(s) is made blind to the exposure status.		No		Yes		No	No	n/a
1.9 Where outcome assessment blinding was not possible, there is some recognition that knowledge of exposure status could have influenced the assessment outcome.		No		No		No	No	No
1.10 The measure of assessment of exposure is reliable.		Yes		No		Yes	Yes	Yes
1.11 Exposure level or prognostic factor is assessed more than once.		n/a		n/a		n/a	Yes	n/a
1.12 Evidence from other sources is used to demonstrate that the method of outcome		Yes		n/a		Yes	Yes	Yes

Risk of Bias Assessment Criteria	Alti et al. (2010)		Coffey et al. (2009)		Grider et al. (2011)		Hayek, Veizi, et al. (2011)	
	Submitter	CEbP	Submitter	CEbP	Submitter	CEbP	Submitter	CEbP
assessment is valid and reliable.								
1.13 The study had an appropriate length of follow-up.		Yes, 3 years		Unclear, 12-month f/u and there may be excess mortality beyond 12 months		Yes, 12 months	Yes	Yes, 12 months
1.14 All groups were followed for an equal length of time (or analysis was adjusted to allow for differences in length of follow-up).		No		Yes		Yes	Yes	Yes
1.15 The main potential confounders are identified and taken into account in the design and analysis		Unclear		No		Unclear	Yes	Yes
1.16 Have confidence intervals been provided?		No		Yes		No	Yes	Yes
1.17 Competing interests of members have been recorded and addressed.		No		Yes		No	Yes	Yes
1.18 Views of funding body have not influenced the content of the study.		Unclear		Unclear		Unclear	Yes	Yes
2.1 How well was the study done to minimize the risk of bias or confounding, and to establish a causal relationship between exposure and effect?		**Poor**	**Fair**	**Poor**		**Fair**	**Good**	**Fair**
2.2 Are the results of this study directly applicable to the patient group targeted by this topic?		Yes		Yes		Yes	Yes	Yes
2.3 Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, are you certain that the overall effect is due to the exposure being investigated?		No		No		No	Yes	Yes
2.4 Comments		Concern for selection bias based on exclusion criteria, unclear how many pts had missing data		Study limitations include lack of information about groups under comparison to know if they are sufficiently similar, lack of analysis of potential confounding factors		Bias may be in favor of intervention, no comparison, no assessment of confounding factors	---	Age has important impact on intrathecal and oral medication dose

Table 4b. *Retrospective Cohort Study Quality Appraisal*

Risk of Bias Assessment Criteria	Kim et al. (2011)		Kongham et al. (2009)		Mekhail et al. (2013)	
	Submitter	CEbP	Submitter	CEbP	Submitter	CEbP
1.1 The study addresses an appropriate and clearly focused question.	*Not included in dossier submission*	Yes	*Not included in dossier submission*	Yes	*Not included in dossier submission*	Yes
1.2 The two groups being studied are selected from source populations that are comparable in all respects other than the factor under investigation.		n/a		n/a		n/a
1.3 The study indicated how many of the people asked to take part did so, in each of the groups being studied.		No		No		n/a
1.4 The likelihood that some eligible subjects might have the outcome at the time of enrollment is assessed and taken into account in the analysis.		n/a		n/a		Yes
1.5 What percentage of individuals recruited into each arm of the study dropped out before the study was completed?		Unclear		0		19/4%
1.6 Comparison is made between full participants and those who dropped out or were lost to follow up, by exposure status.		No		n/a		No
1.7 The study employed a precise definition of outcome(s) appropriate to the key question(s).		Yes		Yes		Yes
1.8 The assessment of outcome(s) is made blind to the exposure status.		No		No		No
1.9 Where outcome assessment blinding was not possible, there is some recognition that knowledge of exposure status could have influenced the assessment outcome.		No		No		No
1.10 The measure of assessment of exposure is reliable.		Yes		Yes		Yes
1.11 Exposure level or prognostic factor is assessed more than once.		n/a		n/a		n/a
1.12 Evidence from other sources is used to demonstrate that the method of outcome assessment is valid and reliable.		Yes		Unclear		Yes
1.13 The study had an appropriate length of follow-up.		Yes, 12 months		Yes, 12 months or more		Yes, 2 years
1.14 All groups were followed for an equal length of time (or analysis was adjusted to allow for differences in length of follow-up).		Yes		Yes		Yes
1.15 The main potential confounders are identified		Unclear		Unclear		Yes

Risk of Bias Assessment Criteria	Kim et al. (2011)		Kongham et al. (2009)		Mekhail et al. (2013)	
	Submitter	CEbP	Submitter	CEbP	Submitter	CEbP
and taken into account in the design and analysis						
1.16 Have confidence intervals been provided?		No		No		Yes
1.17 Competing interests of members have been recorded and addressed.		Yes		Yes		No
1.18 Views of funding body have not influenced the content of the study.		Unclear		Yes		Unclear
2.1 How well was the study done to minimize the risk of bias or confounding, and to establish a causal relationship between exposure and effect?		**Poor**		**Fair**		**Fair**
2.2 Are the results of this study directly applicable to the patient group targeted by this topic?		Yes		Yes		Yes
2.3 Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, are you certain that the overall effect is due to the exposure being investigated?		No		No		No
2.4 Comments		Retrospective review, with data collected from three-year period, data analyzed at one year, unclear if any pts stopped therapy, change in VAS was assessed by intrathecal trial opiate dose, pre-trial opiate dose, baseline VAS and age		Small study (n=13), retrospective data collected through chart review		Retrospective design and exclusion criteria raise concern for selection bias

Table 5. *Case Series Study Quality Appraisal*

Risk of Bias Assessment Criteria	Fluckiger et al. (2008)		Hayes et al. (2012)		Kamran et al. (2001)	
	Submitter	CEbP	Submitter	CEbP	Submitter	CEbP
1.1 The study addresses an appropriate and clearly focused question.	*Not included in dossier submission*	Yes	*Not included in dossier submission*	Yes	*Not included in dossier submission*	Yes
1.2 Were eligibility criteria (inclusion/exclusion) criteria clearly described?		Yes		Yes		Yes
1.3 Were patients recruited or included from more than one center (i.e. multi-center)?		No		No		No
1.4 Was the likelihood that some eligible subjects might have the outcome at the time of enrollment assessed and taken into account in the analysis (pertinent for screening and Yes diagnostic topics)?		n/a		n/a		n/a
1.5 Was the study based on a consecutive sample or other clearly defined relevant population?		Yes		Yes		Yes
1.6 Were patients recruited prospectively?		Yes		Yes		No
1.7 Did all of the individuals enter the study at a similar point in their disease progression? If not, were the results reported separately?		Yes		Unclear		Yes
1.8 Were patients in the sample representative of those seen in practice?		Yes		Unclear, small sample, one center		Unclear
1.9 Were outcomes assessed using objective criteria (i.e. medical records) or was blinding used?		Yes, medical records		No		Yes
1.10 Was follow-up long enough for important events to occur?		Yes		Yes		Yes
1.11 Was there a low dropout or withdrawal rate (<10%)?		Unclear		No, 38% drop-out		No, 20% with missing data
1.12 Were the main potential confounders identified and taken into account in the design and/or analysis?		Unclear		Unclear		Unclear
1.13 Competing interests of members have been recorded and addressed.		No		Yes		No
1.14 Views of funding body have not influenced the content of the study.		No, funded by Medtronic, Inc		Yes		Unclear
2.1 How well was the study done to minimize the risk of bias or confounding, and to establish a causal relationship between exposure and effect?		**Poor**		**Poor**		**Poor**
2.2 Are the results of this study directly applicable to the patient group targeted by this topic?		Yes		Yes		Yes
2.3 Comments		19% of pts underwent IDDS placement for pain		Series of pts who ceased intrathecal therapy for chronic pain		---

Table 6a. *Economic Study Quality Appraisal*

Risk of Bias Assessment Criteria	Biggs et al. (2011)		Bolash et al. (2015)		de Lissovoy et al. (1997)		Dewilde et al. (2009)	
	Submitter	CEbP	Submitter	CEbP	Submitter	CEbP	Submitter	CEbP
1.1 The results of this study are directly applicable to the patient group targeted by this key question.	*Not included in dossier submission*	Yes	Yes	Yes	Yes	Yes	Yes	Yes
1.2 The healthcare system in which the study was conducted is sufficiently similar to the system of interest in the topic key question(s).		Yes, UK	Yes	Yes	Yes	Yes	Yes	Yes, system UK
2.1 The research question is well described.		Yes	---	Yes	---	Yes	---	Yes
2.2 The economic importance of the research question is stated.		Yes	---	Yes	---	Yes	---	Yes
2.3 The perspective(s) of the analysis are clearly stated and justified (e.g. healthcare system, society, provider institution, professional organization, patient group).		Yes, healthcare system	---	No, presumed payer	---	Yes, health care system/payer	---	Yes, healthcare system
2.4 The form of economic evaluation is stated and justified in relation to the questions addressed.		Yes	---	Yes, however, considers only cost of device and not drug	---	Yes	---	Yes
2.5 Details of the methods of synthesis or meta-analysis of estimates are given (if based on a synthesis of a number of effectiveness studies). *or* Details of the design and results of effectiveness study are given (if based on a single study).		Yes, cohort of 12 pts, the comparison group includes pt costs prior to implantation +/- latent period, costs were analyzed two years before and after implantation, QoL using EQ-5D were calculated before and one	---	Yes	---	Yes, evidence of harms is also drawn from studies on cancer pts	---	Yes, model inputs derived from RCT

Risk of Bias Assessment Criteria	Biggs et al. (2011)		Bolash et al. (2015)		de Lissovoy et al. (1997)		Dewilde et al. (2009)	
	Submitter	CEbP	Submitter	CEbP	Submitter	CEbP	Submitter	CEbP
		year after implantation						
2.6 Estimates of effectiveness are used appropriately.		No, QALY assessed one year after implant, but costs assessed for 2 years after, assumes same QALY over the two year period	---	n/a	---	Unclear, months of effectiveness (pain relief in months per system) is included – unclear if this is most appropriate measure)	---	Yes
2.7 Methods to value health states and other benefits are stated.		Yes	---	n/a	---	Yes	---	Yes
2.8 Outcomes are used appropriately.		Yes	---	Yes	---	No, complications estimated from studies for cancer pain	---	Yes
2.9 The primary outcome measure for the economic evaluation is clearly stated.		Yes	---	Yes, longevity	---	Yes	---	Yes, VASPI
2.10 Details of the subjects from whom valuations were obtained are given.		Yes	---	Yes	---	No	---	Yes
2.11 Competing alternatives are clearly described.		Yes, alternative costs assessed 2 years prior to study	---	n/a	---	Yes	---	No, competing alternatives include those with a pump and may be receiving different medications from the pump, however this group is not

Risk of Bias Assessment Criteria	Biggs et al. (2011)		Bolash et al. (2015)		de Lissovoy et al. (1997)		Dewilde et al. (2009)	
	Submitter	CEbP	Submitter	CEbP	Submitter	CEbP	Submitter	CEbP
								well described
2.12 All important and relevant costs for each alternative are identified.		Yes	---	No, post-operative complications costs are not included	---	Yes	---	Yes, alternative costs derived from expert opinion
2.13 Methods for the estimation of quantities and unit costs are described.		Yes	---	No, presumably all from claims data, but not clear	---	Yes	---	Yes
2.14 Quantities of resource use are reported separately from their unit costs.		No	---	No	---	Yes	---	Yes
2.15 Productivity changes (if included) are reported separately.		No	No	n/a	Yes	Yes	Yes	n/a
2.16 The choice of model used and the key parameters on which it is based are justified.		n/a	Yes	n/a	Yes	Yes	Yes	Yes
2.17 All costs are measured appropriately in physical units.		Yes	Yes	Yes	Yes	Yes	Yes	Yes
2.18 Costs are valued appropriately.		Yes	Yes	Unclear	Yes	Yes	Yes	Unclear
2.19 Outcomes are valued appropriately.		Yes	Yes	Unclear	Yes	Unclear	Yes	Unclear, expert opinion used to value alternative options
2.20 The time horizon is sufficiently long enough to reflect all important differences in costs and outcomes.		No, 2 years post-implant, which is a relative short time period over the life of the pump	Yes	n/a	Yes	Yes, 60 months	Yes	Yes, lifetime analysis
2.21 The discount rate(s) is stated.		No	No	No	Yes	Yes, 5%	Yes	Yes
2.22 An explanation is given if costs and benefits are not discounted.		No	No	No	n/a	n/a	Yes	n/a

Risk of Bias Assessment Criteria	Biggs et al. (2011)		Bolash et al. (2015)		de Lissovoy et al. (1997)		Dewilde et al. (2009)	
	Submitter	CEbP	Submitter	CEbP	Submitter	CEbP	Submitter	CEbP
2.23 The choice of discount rate(s) is justified.		n/a	n/a	n/a	Yes	Yes	Yes	Yes
2.24 All future costs and outcomes are discounted appropriately.		No	n/a	n/a	Yes	Yes	Yes	Yes
2.25 Details of currency of price adjustments for inflation or currency conversion are given.		Yes, 2009 British pounds	No	No	n/a	No	Yes	Yes, adjusted to 2006 pounds
2.26 Incremental analysis is reported or it can be calculated from the data.		No	No	n/a	Yes	Yes	Yes	Yes
2.27 Details of the statistical tests and confidence intervals are given for stochastic data.		Yes	Yes	n/a	Yes	No	Yes	Yes
2.28 Major outcomes are presented in a disaggregated as well as aggregated form.		No	---	No	---	Yes	Yes	Yes
2.29 Conclusions follow from the data reported.		Yes	Yes	Yes	Yes	Yes	Yes	Yes
2.30 Conclusions are accompanied by the appropriate caveats.		Yes	Yes	Yes	Yes	Yes	Yes	Yes
3.1 The approach to sensitivity analysis is given.		n/a, no sensitivity analysis	n/a	n/a	Yes	Yes	Yes	Yes
3.2 All important and relevant costs for each alternative are identified.		n/a	n/a	n/a	Yes	Yes	Yes	Yes
3.3 An incremental analysis of costs and outcomes of alternatives is performed.		n/a	No	n/a	Yes	Yes	Yes	Yes
3.4 The choice of variables for sensitivity analysis is justified.		n/a	n/a	n/a	Yes	Yes, all	Yes	Yes
3.5 All important variables, whose values are uncertain, are appropriately subjected to sensitivity analysis.		n/a	n/a	n/a	Yes	Yes	Yes	Unclear
3.6 The ranges over which the variables are varied are justified.		n/a	n/a	n/a	Yes	Yes	Yes	Unclear
4.1 Competing interests of members have been recorded and addressed.		Yes	Yes	Yes	Yes	No	Yes	Yes, two authors employees of Eisai
4.2 Views of funding body have not influenced the content of the study.		Yes	Yes	Yes	Unclear	No, Medtronic funded	Yes	No, funded by Eisai, maker of

Risk of Bias Assessment Criteria	Biggs et al. (2011)		Bolash et al. (2015)		de Lissovoy et al. (1997)		Dewilde et al. (2009)	
	Submitter	CEbP	Submitter	CEbP	Submitter	CEbP	Submitter	CEbP
								ziconotide
5.1 How well was the study done to minimize bias?		**Poor**	**Good**	**Poor**	**Good**	**Fair**	**Good**	**Fair**
5.2 If coded as fair or poor, what is the likely direction in which bias might affect the study results?		Bias toward intrathecal infusion pump, see Table 5	Retrospective	Bias toward intrathecal infusion pump, see Table 5	---	Bias may be introduced by including data of harms from cancer patients, it is unclear how this would impact the results	Ziconotide compared with best standards of care control group from RCT	Bias toward intrathecal ziconotide, see Table 5
5.3 Other reviewer comments:		---	---	---	---	---	---	---

Table 6b. *Economic Study Quality Appraisal*

Risk of Bias Assessment Criteria	Guillemette et al. (2013)		Kumar et al. (2002)		Kumar et al. (2013)		Thrasher & Fisher (2013)	
	Submitter	CEbP	Submitter	CEbP	Submitter	CEbP	Submitter	CEbP
1.1 The results of this study are directly applicable to the patient group targeted by this key question.	Yes	Yes, intrathecal device compared to conventional pain therapy	Yes	Yes, intrathecal device compared to conventional pain therapy	Yes	Yes	---	Yes, intrathecal device for pain pts (does not specify malignant/non-malignant)
1.2 The healthcare system in which the study was conducted is sufficiently similar to the system of interest in the topic key question(s).	Yes	Yes	Yes	Yes	Yes	Yes, Canadian healthcare system	---	Yes, US
2.1 The research question is well described.	---	Yes	---	Yes	---	Yes	---	Yes
2.2 The economic importance of the research question is stated.	---	Yes	---	Yes	---	Yes	---	Yes
2.3 The perspective(s) of the analysis are clearly stated and justified (e.g. healthcare	---	Yes, healthcare system	---	Yes, healthcare system	---	Yes, healthcare	---	Yes, societal, direct medical

Risk of Bias Assessment Criteria	Guillemette et al. (2013)		Kumar et al. (2002)		Kumar et al. (2013)		Thrasher & Fisher (2013)	
	Submitter	CEbP	Submitter	CEbP	Submitter	CEbP	Submitter	CEbP
system, society, provider institution, professional organization, patient group).						system		costs (all costs, not just pain)
2.4 The form of economic evaluation is stated and justified in relation to the questions addressed.	---	Yes	---	Yes	---	Yes	---	Yes
2.5 Details of the methods of synthesis or meta-analysis of estimates are given (if based on a synthesis of a number of effectiveness studies). *or* Details of the design and results of effectiveness study are given (if based on a single study).	---	Yes, based on a single cohort study and used claims data to identify cohort, pt selection was based on claims data	---	Yes, based on RCT of pts who initially failed spinal cord stimulation therapy	---	Yes	---	Yes, retrospective cohort of pts with private medical insurance, costs are analyzed in the 12 months preceding and following implantation
2.6 Estimates of effectiveness are used appropriately.	---	n/a	---	n/a	---	Yes, data on effectiveness are not clearly laid out, HRQoL surveys were provided for each group at 6 months	---	n/a
2.7 Methods to value health states and other benefits are stated.	---	n/a	---	n/a	---	Yes	---	n/a
2.8 Outcomes are used appropriately.	---	Unclear, outcomes are repeated in 6 year cycles to account for ave pump life of 6 yrs, repeated 5x over the course of 30 yrs	---	Yes	---	Yes	---	Yes
2.9 The primary outcome measure for the	---	Yes, cost	---	Yes, cost	---	Yes	---	Yes, medical costs

Risk of Bias Assessment Criteria	Guillemette et al. (2013)		Kumar et al. (2002)		Kumar et al. (2013)		Thrasher & Fisher (2013)	
	Submitter	CEbP	Submitter	CEbP	Submitter	CEbP	Submitter	CEbP
economic evaluation is clearly stated.								
2.10 Details of the subjects from whom valuations were obtained are given.	---	Yes, based on claims data – codes that were for neoplasms or spastic conditions were excluded	---	Yes	---	Yes		Yes, in general, pts were groups in diagnosis, and if there was inaccurate coding, they may have been placed in wrong group, it is unclear what percentage of pts had malignant pain
2.11 Competing alternatives are clearly described.		Yes, patient is her own control, alternative are costs incurred prior to implantation	---	Yes, conventional pain therapy group is a strength of the study	---	Yes, the comparison group includes individuals who failed a trial of intrathecal therapy or refused intrathecal therapy, this group is not a fair comparison	---	No
2.12 All important and relevant costs for each alternative are identified.	---	n/a	---	Yes	---	Yes	---	n/a
2.13 Methods for the estimation of quantities and unit costs are described.	---	Yes	---	Yes	---	Yes	---	n/a
2.14 Quantities of resource use are reported separately from their unit costs.	---	No	---	Yes	---	No	---	No
2.15 Productivity changes (if included) are	Yes	No	Yes	Yes	Yes	No	---	No

Risk of Bias Assessment Criteria	Guillemette et al. (2013)		Kumar et al. (2002)		Kumar et al. (2013)		Thrasher & Fisher (2013)	
	Submitter	CEbP	Submitter	CEbP	Submitter	CEbP	Submitter	CEbP
reported separately.								
2.16 The choice of model used and the key parameters on which it is based are justified.	Yes	Yes	Yes	Yes	Yes	Yes	---	n/a
2.17 All costs are measured appropriately in physical units.	Yes	Yes	Yes	Yes	Yes	Yes	---	Yes
2.18 Costs are valued appropriately.	Yes	Yes, taken from claims data	Yes	Yes	Yes	Unclear, the unit cost and quantity are not listed for each group	---	Yes
2.19 Outcomes are valued appropriately.	Yes	Unclear, claims data may miss some important outcomes	Yes	Yes	Yes	Unclear, concern for selection bias which would make outcomes different	---	n/a
2.20 The time horizon is sufficiently long enough to reflect all important differences in costs and outcomes.	Yes	Yes, 30 years	Yes	Unclear, 5 years, then also calculated at 10 years	Yes	Yes, 10 years	---	No, one year pre and post impant
2.21 The discount rate(s) is stated.	Yes	Yes, 3%	No	No	Yes	Yes, 5%	---	n/a
2.22 An explanation is given if costs and benefits are not discounted.	Yes	n/a	No	No	Yes	n/a	---	n/a
2.23 The choice of discount rate(s) is justified.	Unclear	Yes	n/a	n/a	Yes	Yes	---	n/a
2.24 All future costs and outcomes are discounted appropriately.	n/a	Yes	n/a	No	Yes	Yes	---	No
2.25 Details of currency of price adjustments for inflation or currency conversion are given.	No	Yes	Yes	Yes, no adjustments for inflation are made	Yes	Yes, 2011 Canadian dollars	---	Yes, 2011 US dollars
2.26 Incremental analysis is reported or it can be calculated from the data.	Yes	Yes	No	Yes	Yes	Yes	---	No
2.27 Details of the statistical tests and confidence intervals are given for stochastic	Yes	No	Yes	Yes	Yes	No	---	Yes

Risk of Bias Assessment Criteria	Guillemette et al. (2013)		Kumar et al. (2002)		Kumar et al. (2013)		Thrasher & Fisher (2013)	
	Submitter	CEbP	Submitter	CEbP	Submitter	CEbP	Submitter	CEbP
data.								
2.28 Major outcomes are presented in a disaggregated as well as aggregated form.	Yes	Yes	Yes	Yes	Yes	No	---	No
2.29 Conclusions follow from the data reported.	Yes	Yes	Yes	Yes	Yes	Yes	---	Yes
2.30 Conclusions are accompanied by the appropriate caveats.	Yes	No, not all caveats	Yes	No	Yes	No, the possibility of selection bias is not mentioned, Yes study lacks internal validity in additional to external validity (small sample, single center)	---	Yes
3.1 The approach to sensitivity analysis is given.	Yes	Yes	Yes	No	Yes	Yes	---	n/a, no sensitivity analysis
3.2 All important and relevant costs for each alternative are identified.	Yes	Unclear	Yes	Unclear	Yes	Yes	---	n/a
3.3 An incremental analysis of costs and outcomes of alternatives is performed.	No	Yes	No	Unclear	Yes	Yes	---	n/a
3.4 The choice of variables for sensitivity analysis is justified.	n/a	Yes	No	Yes	Yes	Yes	---	n/a
3.5 All important variables, whose values are uncertain, are appropriately subjected to sensitivity analysis.	n/a	Unclear, selected 3 variables for sensitivity analysis	No	Unclear, only 3 variables were subject to sensitivity analysis: pump cost, pump lifespan, complication costs	Yes	Yes	---	n/a

Risk of Bias Assessment Criteria	Guillemette et al. (2013)		Kumar et al. (2002)		Kumar et al. (2013)		Thrasher & Fisher (2013)	
	Submitter	CEbP	Submitter	CEbP	Submitter	CEbP	Submitter	CEbP
3.6 The ranges over which the variables are varied are justified.	n/a	Unclear	Yes	Unclear	No	Yes	---	n/a
4.1 Competing interests of members have been recorded and addressed.	Yes	No, some study authors from Medtronic, and director of health and policy of Medtronic helped in study design/analysis	Yes	Yes	Yes	Yes, lead author is a consultant for Medtronic	---	Yes
4.2 Views of funding body have not influenced the content of the study.	Yes	No, funded by Medtronic	Yes	Unclear	Unclear	Unclear	---	Unclear, one author is consultant and speaker for Medtronic
5.1 How well was the study done to minimize bias?	**Good**	**Fair**	**Good**	**Fair**	**Good**	**Poor**		**Fair**
5.2 If coded as fair or poor, what is the likely direction in which bias might affect the study results?	---	Bias toward intrathecal infusion pump. See Table 5.	RCT with CPT as control	Bias toward intrathecal infusion pump. See Table 5.	---	Bias toward intrathecal infusion pump. See Table 5.	---	Unclear. Study objective in that it analyzes cost 12 months pre and post implant without making comparison to pts who are managed in other ways, the study reports high costs of medical care in pts treated with intrathecal drug devices, but conclusions regarding the underlying

Risk of Bias Assessment Criteria	Guillemette et al. (2013)		Kumar et al. (2002)		Kumar et al. (2013)		Thrasher & Fisher (2013)	
	Submitter	CEbP	Submitter	CEbP	Submitter	CEbP	Submitter	CEbP
								reasons for those high costs cannot be made
5.3 Other reviewer comments:		---		---		---	---	---

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