Washington State Health Care Authority

Health Technology Assessment Program

Health Technology Clinical Committee
IDDS Pumps

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Washington's Health Technology Assessment Program Background

- **Part of Governor's 2006 Five point health strategy for state to lead by example**
  - **Emphasize evidence-based health care**

    http://www.hca.wa.gov/contf/doc/GovGregoireHealthBrief.pdf

- **Program Purpose: Achieve better health by paying for technologies that work**
  - Better health with better information: investigate what works and maintain a centralized website.
  - Open and transparent process: publish process, criteria, reports, and committee decisions in public meeting.
  - Eliminate Bias: contract for independent evidence report and independent clinical committee.
  - Promote consistency: state agencies rely on a single, scientifically based source.
  - Flexible: review evidence regularly to ensure update information is included.

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Why Health Technology

Health Care Context

- **Part of an overall strategy**
- **Medical technology is a primary driver of cost**
  - The development and diffusion of medical technology are primary factors in explaining the persistent difference between health spending and overall economic growth.
  - Some health experts arguing that new medical technology may account for about one-half or more of real long-term spending growth.
    Kaiser Family Foundation, March 2007: **How Changes in Medical Technology Affect Health Care Costs**
- **Medical Technology has quality gaps**
  - Medical technology diffusing without evidence of improving quality Highly correlated with misues, overutilization, underutilization.
    Cathy Schoen, Karen Davis, Sabrina K.H. How, and Stephen C. Schoenbaum, "U.S. Health System Performance: A National Scorecard," *Health Affairs*, Web Exclusive (September 20, 2006): w459

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Washington State Health Care Authority

HTA Goal

Outcome: Pay for What Works

- Coverage decisions:
  - scientifically based
  - use transparent process, and
  - consistent across state health care purchasing agencies
- Formal, systematic process to identify, review, and cover appropriate health care technologies.
  - Is it safe?
  - Is it effective?
  - Does it provide value (improve health outcome)?

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Washington State Health Care Authority

Process Overview

1. HCA Administrator Selects Technology

Nominate, Review, Public Input, Prioritize

Semi-annual

2. Vendor Produce Technology Assessment Report

Key Questions and Work Plan, Draft, Comments, Finalize

2-8 Months

3. Clinical Committee makes Coverage Determination

Review report, Public hearing

Meet Quarterly

4. Agencies Implement Decision

Implements within current process unless statutory conflict

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Hierarchy of Evidence

Best: Meta-analysis of large randomized head-to-head trials.

Large, well-designed head-to head randomized controlled clinical trials (RCT):

- Long-term studies, real clinical endpoints
- Well accepted intermediates
- Poorly accepted intermediates

Smaller RCTs, or separate, placebo-controlled trials

Well-designed observational studies, e.g., cohort studies, case-control studies

Safety data without efficacy studies

Case series, anecdotes

Least: Expert opinion, non-evidence-based expert panel reports, and other documents with no direct clinical evidence

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Evidence for use in Policy Decisions

Different Data Sources

- Efficacy
  - How technology functions in "best environments"
    - Randomized trials-distinguish technology from other variables
    - Meta-analysis
- Effectiveness
  - How technology functions in "real world"
    - Population level analyses
    - Large, multicenter, rigorous observational cohorts (consecutive pts/objective observers)
- Safety
  - Variant of effectiveness
    - Population level analyses
    - Case reports/series, FDA reports
- Cost
  - Direct and modeled analysis
    - Administrative/billing data (charge vs cost)
- Context
  - Mix of historic trend, utilization data, beneficiary status, expert opinion

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Chronic Non-Cancer Pain (CNCP)

- CNCP is an important and common medical concern worldwide defined as pain lasting beyond the normal time of healing, and three months or longer. International Association for Study of Pain (IASP)
- Most common source is low back pain
- prevalence rates of chronic pain (any severity) to be as high as 55% and an estimated 9% of Americans have moderate to severe CNCP (ECRI Review)
- Most find adequate relief from conservative therapy or treatment of underlying/co-morbid condition (ECRI Review)
- Estimated 1% to 20% have pain resistant to treatment or unacceptable side effects ((Williams et al. INHATA Review, 2000)

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Chronic Non-Cancer Pain

- Chronic pain is burdensome – discomfort, decrease in quality of life, daily activities, function, and employment
- Chronic pain is costly due to high prevalence, chronicity, co-morbidities present, multiple modalities and clinician supervision often needed
- CNCP treatment goal to reduce pain, improve quality of life, and resume daily activities without substantial side effects

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Intrathecal Drug Delivery Systems (IDDS)

- IDDS first introduced for CNCP treatment in late1970's with realization that spinal cord was important in pain transmission. (Williams et al. INHATA Review, 2000)
- Improvements in intrathecal drugs and pump systems to modern IDDS occurred throughout 1980 and 1990s (Williams et al. INHATA Review, 2000)
- IDDS includes catheter and totally implantable, externally programmable pump

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IDDS Technology

- IDDS used for diabetes, spasticity, and cancer pain not at issue and fully covered by all agencies
- IDDS for CNCP seeks to replace the route of opioid administration to achieve better pain control with fewer adverse effects (Williams et al. INHATA Review, 2000)
- IDDS treatment is invasive, prone to side-effects and complications, costly, and requires a large amount of technical support (Williams et al. INHATA Review, 2000)
- For patients with pain resistant to all conventional therapies this treatment may be beneficial (Williams et al. INHATA Review, 2000)

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IDDS Potential Benefits

- Lower dose and effective pain relief by delivery of opioids direct to spinal cord (instead of systemic oral/injected)
- Fewer side effects due to lower dose/direct administration
- Better pain control leads to:
  - Improved quality of life
  - Improved functional status
  - Improved employment status
- Reduced addiction/tolerance
- Patient convenience

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Potential Drawbacks

- Invasive procedure that is an additional method to deliver opioids
  (not replacement or different treatment mechanism for individuals with chronic pain)
- Tolerance and dose escalation of infused and adjudavent oral medications
- Safety Issues
  - Overdose of infused medications
  - Infused drug side effects
  - Device/ Mechanical pump complications
  - Surgical Complications
- Permanent implantation implications
  - Non-life threatening condition with unknown resolution
  - Generally middle age candidates
  - Maintenance and revisions required –risks with each surgery; long term patient and provider commitment
- Costs and specialty provider availability for long term

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Agency Prioritization

- **Safety concern: High**
  - Drug tolerance and drug-related side effects
  - Device related complications
  - Multiple follow-up services
  - Overdose and surgical complications
- **Efficacy concern: Medium**
  - Many patients still experience chronic moderate to severe pain even with implant.
  - No improvement in disability or employment status
  - Removal rate for intolerance or lack of effect
- **Cost Concern: Low**
  - Individual cost for technology is relatively high, but implantation for chronic pain utilization is currently very low.
  - However, current utilization/dissemination may change if widely permitted and
  - population with chronic pain is significant

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Medicare Coverage Policy

Medicare has a national coverage decision for infusion pumps (manual section 280.14) that covers all uses (permanent and temporary, cancer, diabetes, non-cancer pain).

Under this policy, permanent intrathecal pump implantation is covered with criteria:

- Life expectancy of at least three months
- Unresponsive to less invasive medical therapy, such as systemic opioids and attempts to correct underlying physical and psychological abnormalities
- Successful intraspinal opioid trial, defined by acceptable pain relief and side effects and their impact on daily living, and patient acceptance

A national coverage decision for infusion pumps (manual section 280.14) was issued in February 1994 as durable medical equipment. The latest version of the policy was implemented December 17, 2004, and made effective February 18, 2005. This determination included implantable infusion pumps for epidural or intrathecal administration of opioid drugs for chronic non-cancer pain.

This NCD; however, was based on a technology assessment completed in 1994 by the Office of Health Technology Assessment (OHTA) and used the only available literature which was from 1984-1992.

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IDDS Clinical Practice Guidelines

Organization	Date	Outcome	Evidence Cited?
American Society of Interventional Pain Physicians (Boswell et. al)	2007	"Evidence for implantable intrathecal infusion systems is strong for short term improvement in pain of malignant or neuropathic pain. The evidence is moderate for long term management of chronic pain."	Y
Sisken Hospital for Physical Rehabilitation (Sanders et. al)	2005	"Studies and systematic reviews regarding the efficacy of infusion pumps and spinal cord stimulators have increased. Thus far, they have not met the current criteria for adequate supportive evidence to recommend the application to CPS (chronic pain syndrome) patients".	Y
International Research Foundation for RSD/CRPS (Kirkpatirck et. al)	2003	No conclusion offered, however authoirs note that "morphine pumps" have not been clinically shown to be superior to oral morphine.	Not reported

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Washington State Health Care Authority

IDDS Pumps

Questions?

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Washington State Health Technology Assessment
Intrathecal Drug Delivery Discussion

August 15, 2008

William Fehrenbach, John Loeser, MD, David Caraway, MD

Mary Owens, MD, Mike Baca, Scott Guillemette

Agenda

- **Contextual Overview, Request for Subcommittee** (1 minute) — **W. Fehrenbach**
  - Unique complexities, legislative intent, focus on safety questions, request for Pain Subcommittee
  - "Presumption of Correctness" of Medicare, National Medical Society/Patient Group Guidelines, Insurance Covg.
  - Unique and sick population that has exhausted all other treatment options
- **Mitigating Risk Strategies and Status**
  - Dr. John Loeser Experience, Thoughts (5 minutes via teleconference) — **J. Loeser, M.D.**
  - Dr. Caraway Experience, Thoughts, How to Collaborate to Best Ensure Patient Safety (15 minutes) — **D. Caraway, M.D.**
- **Medical and Data Issues** (3 minutes) — **M. Owens, M.D.**
  - Unique and sick population that has exhausted all other treatment options
  - FDA MAUDE Database Limitations
  - Industry "event" increases overall
  - ISPR – Highlights of Updated Information
  - Patient Deaths, Educational Brief, Adverse Outcomes
- **FDA Warning Letter, Product Issues, Safety Alerts and Solutions** (3 minutes) — **M. Baca**
- **Cost Effectiveness** (3 minutes) — **S. Guillemette**
  - New actuarial analysis from Reden & Anders in Response to ECRI Questions

Introductions and Contextual Overview

William Fehrenbach, Medtronic Director State Government Affairs
(One Minute)

- **Context**
  - Provide background and context. There are three areas that we want to cover:
    - Therapy Importance, Impact for Patients with No Other Options
    - Mitigating Risks – Ensuring Patient Safety
    - Medtronic's Commitment to Quality and Safety
  - Through an extensive review process (Pre-Market Approval) the FDA has determined the benefits outweigh the risks of this therapy. We agree there are associated risks - most productive discussion is to substantively focus on how to mitigate and minimize risks wherever possible.
  - We believe that given both the unique complexities involved in this discussion, and with the fact that HTA leadership acknowledges that the legislative intent of this program did not envision these types of discussions, that an Interventional Pain "Advisory Group" should be convened to best sort through these complexities and to establish how to best ensure patient safety moving forward, and are requesting same be convened and stand ready to assist in any appropriate manner. RCW 70.14.110 (2)(c); WAC 182-55-045
  - Will do our best to directly answer any and all questions to the best of our ability but time is very limited for public testimony today so we would ask that questions be deferred until after panel presentation and all public testimony is complete. We are willing to stay all day, or to be involved in any Advisory Group discussions, to answer any and all questions.

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Medicare and National Expert Society Guidelines "Presumed Correct"

- **RCW 70.14.110 (3) states that HTA's reviews and determinations "shall be consistent with decisions made under the federal Medicare program and in expert treatment guidelines, including those from specialty physician organizations and patient advocacy organizations unless the committee concludes, based on its review of the systematic assessment, that substantial evidence regarding the safety, efficacy, and cost-effectiveness of the technology supports a contrary determination."**
  - **POSITIVE NATIONAL MEDICARE COVERAGE DECISION: CMS has issued an affirmative National Coverage Decision (NCD) for coverage of IDDS for non cancer pain.**
  - **We believe this is the first therapy, intervention, test that HTA is reviewing that has a positive National Medicare Coverage Decision as well as support from national expert medical societies and patient advocacy groups through position statements, guidelines and other work.**
  - **Overwhelming support for this therapy in appropriate situations.**
  - **For patients that have no other options, this therapy is the standard of care.**

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Supported by Societies and Patient Organizations

- ***Evidence Based Treatment Guidelines***
  - *American Society of Interventional Pain Physicians (3,000 members)*
  - *Official Disability Guidelines (used in at least 19 states), continually updated*
  - *Workers Compensation State Regulations*
    - *Washington and all other 49 state currently provide coverage*
    - *California DWC Proposal to be adtoped in September, supporting appropriate coverage for IDDS for non-cancer pain*
    - *Minnesota in midst of updating and adopting new EBM supported IDDS coverage policy for non-cancer pain*
    - *Delaware adopted EBM guidelines June 2008 including apropriate coverage for IDDS for non-cancer pain*
  - *Millman, Interqual*
- ***Other physician organizations whose members are actively involved in the implantation of IDDS for non-cancer pain:***
  - *American Academy of Pain Medicine*
  - *International Spine Intervention Society*
  - *North American Neuromodulation Society*
  - *International Spine Society*
  - *American Society of Anesthesiologists*
  - *American Association of Neurological Surgeons/CNS Section of Pain*
  - *American Society or Regional Anesthesia and Pain Medicine*
  - *American Pain Society*
- *Patient advocacy groups that support appropriate coverage of IDDS for non-cancer pain:*
  - *American Pain Foundation (86,000 members) (Patient Organization)*
  - *Washington Alaska Pain Initiative (Patient Organization)*
- ***Additional government and private payor coverage policies, additional attached national list***
  - *Civilian Health and Medical Program of the Department of Veterans Affairs*
  - *TRICARE*
  - *Premera, Regence Coverage Policies; Group Health Case-by-Case Coverage*

Therapy, Evidence, Patient Safety

(5 minutes)

John Loeser, MD, University of Washington

Calling in from Europe via Teleconference

Phone number to call:

Dial the country code (00) and then 1 plus 309 946 5000

Code: 9461464

Risk Mitigation Strategies

(15 minutes)

David L. Caraway, MD, PhD

Center for Pain Relief Tri-State

Saint Mary's Regional Neuroscience Center

Huntington, WV

AMDG *3/2007*

Interagency Guideline on Opioid Dosing for Chronic Non-Cancer Pain

- **Reasonable Guidelines are in place**
- **No discussion regarding impact of route of delivery**
- **Long acting, sustained release, non-compounded opioids generally recommended with referral to pain management at does exceeding 120 MED**

Intrathecal Opioids

- **Requires same strategies as systemic delivery**
  - Early titration to achieve analgesia and goals of therapy
  - Careful consideration of dose increases
  - Maintain moderate doses
  - Physician remains in control of dosing
  - Monitor for side effects, efficacy
  - Adjuvants

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Intrathecal Opioids

Advantages:

- **Achieves steady-state, around the clock dosing**
- **Reduced side effects**
  - Hormonal effects and edema may be exceptions
- **Adjuvants**
- **May result in reduction in longitudinal costs**
- **Compliance**
  - Can provide patient activated rescue dosing
  - Eliminate systemic opioids

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AMDG

- **L&I data shows that between 1996 and 2002 there were 32 deaths among injured workers where an accidental overdose of prescription opioids, or narcotics, was confirmed.**
- **Statewide, deaths involving prescription opioids — sometimes used illegally — increased by more than 800 percent from 1995 to 2004.**
- **Prescription opioid related deaths now exceed non-prescription opioid related deaths.**

Franklin AMDG 3/2007

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IDD – Risk Mitigation

- **Early in 2006, Medtronic became aware of an apparent increase in the rate of spontaneous reports of patient death with intrathecal drug therapy**
- **A total of nine patient deaths within three days after the initiation – or re-initiation following interrupted use – of intrathecal opioid therapy for pain.**

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Risk Mitigation

"The available evidence indicates that the infusion systems operated normally."

- Relatively high initial doses

- Respiratory depressant effects of intrathecal opioids All nine deaths involved patients who were just started on intrathecal opioid therapy, or for whom the therapy was restarted after weeks of interruption.

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Risk Mitigation

- Insufficient patient monitoring: **Seven of the patients were released from the hospital within 24 hours after *initiation* of intrathecal opioid therapy for pain or after *re-initiation* of intrathecal therapy following interrupted use.**
- Concomitant medications: **Seven patients were prescribed, administered in-hospital, or self-administered systemic opioid and/or sedative drugs. Those concomitant medications may have amplified the respiratory depressant effects of the intrathecal opioids.**
- Co-morbid risk factors: **Several patients had risk factors for respiratory depression that included pulmonary disease, severe obesity, and/or advanced age.**

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White Paper Recommendations

Co-administration of medications

Closely monitor patients at initiation or

re-initiation of intrathecal therapy***.***

"Patients should be monitored in an adequately equipped facility for sufficient time"

The Infumorph package insert states, "*The facility must be equipped with resuscitative equipment, oxygen, naloxone injection, and other resuscitative drugs."*

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AMDG

Principles for prescribing opioids

"Do not combine opioids with sedative hypnotics, benzodiazepines, or barbiturates"

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Principles for prescribing opioids:

"Be cautious about using opioids with conditions that may potentiate opioid adverse effects (including COPD,CHF,sleep apnea, alcohol or substance abuse, elderly,or history of renal or hepatic dysfunction"

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White Paper Recommendations

"Physicians also should be aware of the complexity and uncertainty involved in converting a systemic opioid dose to an equianalgesic intrathecal dose"

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Infumorph package insert

Intrathecal Opioids

Disadvantages:

- **More invasive**
- **More difficult to discontinue therapy**
- **Acquisition costs**
- **If positioned as a salvage therapy for patients who have failed but remain on high dose systemic opioids outcomes are diminished**

Do we need oral opioids after pump implant?

- **Vertebral Compression Fractures, N=24**
- **Failed systemic opioids**
- **Compare before implant to one year follow up**
  - VAS, DW, ambulation, PHS
- **Results**
  - None required systemic opioids
  - All showed significant improvement

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Dose Escalation

- **Tolerance**
  - Physiological, role of age
- **Opioid Induced Hyperalgesia**
  - Solid evidence in animal models
  - Emerging clinical data
- **Perception**
  - Goals of therapy
- **Disease progression**

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QUALITY OF PAIN

Patient Selection – positive factors

- Cancer
- Diffuse pain, eg Rh. Arthritis
- Elderly axial spinal pain
- Mechanical, nociceptive back pain, documented etiology
- Good analgesia with systemic opioids but intolerable side effects

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Results of Change in Route of Opioid Administration

Parameter	At Crossover	Crossover + 1 Month	% Change
Pain			
VAS	5.78 ± 2.92	4.89 ± 2.77	15.4
Pain on Average	6.39 ± 1.85	4.94 ± 2.24	22.7
Patient Quality of Life			
SF-12 mental	36.45 ± 6.16	37.13 ± 7.54	-1.9
SF-12 physical	24.25 ± 4.38	24.9 ± 6.86	-2.7
$BPI_{Interference\ with\ life}$	6.83 ± 1.44	6.37 ± 2.50	6.7
$BPI_{Enjoyment\ of\ life}$	6.83 ± 2.18	6.39 ± 2.77	6.4
Caregiver QOL			
Caregiver QOL	5.6 ± 1.41	5.66 ± 1.70	-1.1
Opioid Toxicity			
NCI Toxicity	7.06 ± 4.87	3.71 ± 4.43	47.5

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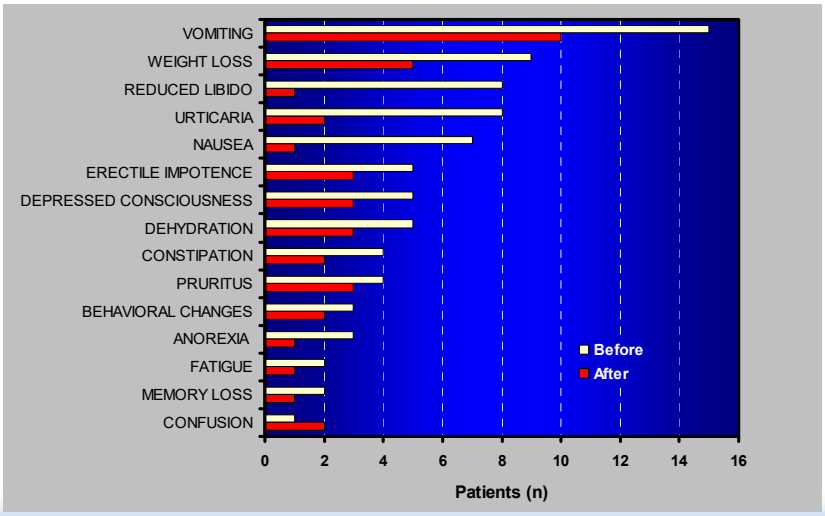
Smith, T. J Clin Oncology, 2002

Prevalence of Opioid Side Effects



Smith, T. J Clin Oncology, 2002

QUALITY OF PAIN

Patient Selection – negative factors

Minimal baseline pain with intermittent severe pain

Poorly defined etiology

Poor compliance to previous therapies

Poor response to escalating doses of opioids

Young age

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Goals of Therapy

- **Create a written document with specific goals *eg:***
  - Manageable constipation
  - Gardening, shopping, holding grandchildren
  - Increased range of motion, ambulation
  - Reduced hospital, ER visits

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Psychological Evaluation

- **Consider recommendations and treat if indicated - *prior to trial***
- **Ability to understand and perceive benefits -- appropriate expectations**
- **Major active psychosis, current drug addiction, some personality disorders, cognitive deficits, progressive organic brain disorders, suicidal, homicidal behavior**

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Continuous vs single shot and intermittent bolus

- **Titration**
- **Interpreting adverse events**
- **Multiple procedures**
- ***Does not model steady-state characteristics of intended therapy***

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Continuous Epidural vs Continuous Intrathecal Screening

	Advantages	Disadvantages
Intrathecal	More closely approximates pharmacodynamics of system to be implanted Does not require epidural space (fusion, mets)	Increased risk of: PDPH CSF leak Serious infection Overdose Neurological complication during placement
Epidural	May allow outpatient Management Extended trials Less risks	Less predictive? Risk of migration to SAS

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Polyanalgesia Consensus Conference 2007

2007 POLYANALGESIC ALGORITHM FOR INTRATHECAL THERAPIES

Line #1:	**(a)** morphine	↔ **(b)** hydromorphone	↔ **(c)** ziconotide
Line #2:	**(d)** fentanyl	↔ **(e)** morphine/hydromorphone + ziconotide	↔ **(f)** morphine/hydromorphone + bupivacaine/clonidine
Line #3:	**(g)** clonidine	↔ **(h)** morphine/hydromorphone/fentanyl bupivacaine +/clonidine +ziconotide	
Line #4:	**(i)** sufentanil	↔ **(j)** sufentanil + bupivacaine +/ clonidine +ziconotide	
Line #5:	**(k)** ropivacaine, buprenophine, midazolam meperidine, ketorolac		
Line #6	***Experimental Drugs*** gabapentin, octreotide, conpeptide , Neostigmine, Adenosine, XEN2174, AM336, XEN, ZGX 160		

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Recommended Maximum Intrathecal Dosages and Concentrations*

Drug	Dosage (mg/day)	Concentration(mg/ml)
Morphine	**15**	**20**
Hydromorphone	**4**	**10**
Fentanyl	**2**	**No known upper limit**
Bupivacaine	**30**	**40**
Clonidine	**1.0**	**2.0**

These represent general recommendations and are dependent upon the specific patient and the clinical experience of the physician and thus, maximum dosage and/or concentrations may vary from these.

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Special Cases in Chronic Pain Management

- **Single-agent therapy insufficient**
  - Bupivacaine plus opioid
  - Clonidine plus opioid
  - Ziconotide plus opioid
- **End of Life (Cancer, AIDS)**
  - Midazolam
  - Ketamine
  - Tetracaine
  - Droperidol
- **Spasticity as a major component of pain**
  - Baclofen

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Special Cases in Chronic Pain Management

- **Adjuvant Medications**
  - Requires reformulation to change dosing of single component
  - Addition of single agent at a time recommended
  - Complex mixtures are generally not well studied
  - Requires compounding to achieve therapeutic dose
    - Formulation errors
    - Contamination
    - Dosing errors, increased complexity
    - Side effects / toxicities

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An Approach

- **Perform and document history and PE**
- **Document reasonable etiology**
- **Document failure of conservative therapy**
- **Psychological evaluation**
- **Create written goals of therapy**
- **Consider discontinuation of systemic opioids prior to trial**

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An Approach

- **Perform inpatient catheter trial**
  - Consistent with Medicare guidelines
  - Discontinue or dramatically reduce systemic opioids during trial
  - Trial with single opioid
    - Generally morphine or hydromorphone
  - Document achievement of goals of therapy
  - Document tolerable side effect

An Approach

- **Perform implant as overnight stay**
  - Start with lower than anticipated analgesic dose
- **Discontinue systemic opioids**
- **Titrate to achieve goals within 6- 8 weeks of initiation of opioid therapy**
  - 20 – 30% dose increases
- **Document attainment of goals**

An Approach

- **Failure to achieve moderate stable dose warrants re-examination of treatment plan**
  - Trial of adjuvant while holding opioid dose steady
  - Episodic pain and “rescue dosing”
  - Rotation of opioids
  - Reduction or discontinuation
  - Surveillance
    - Progression of disease
    - Complications eg: IM, catheter failure

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INTRATHECAL THERAPY FUTURE

- **Novel Agents**
  - Improved efficacy
  - Elimination of tolerance and withdrawal
- **Improved devices**
- **IT activity related rescue doses**
- **Ultra low dose IT therapy**
  - Potential for decreased tolerance, OIH
  - Enhanced patient satisfaction
  - Elimination of all oral agents

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Context: Patient Population for IDSS

Mary Owens, MD, Medtronic Regulatory Medical Director
(Three Minutes)

- **Extremely sick patient population with intractable pain**
  - These treatments must be balanced against the unreasonable alternative of no further treatment which would leave these very ill patients in chronic, intractable pain or with severe untreated spasticity. In fact, to put these illnesses in perspective, a study by Brown[1] et al demonstrated that IDDS candidates have poorer physical functioning and lower health-related quality of life scores than patients with congestive heart failure, Type II diabetes, rheumatoid arthritis, and patients actively suffering a migraine headache.
- **Already tried and exhausted all other treatment**
  - Pain is not responsive to over the counter analgesics, oral systemic analgesics, antidepressants and membrane stabilizing drugs
  - Unsatisfactory response to systemic opioids due to lack of therapeutic effect or intolerable side effects
  - Medtronic's own data base shows that these patients also tend to have multiple medical conditions in addition to the condition requiring therapy for pain

[1]*Brown J. Klapow J, Doleys D, et al. Disease-specific and generic health outcomes: A model for the evaluation of long-term intrathecal opioid therapy in non-cancer low back pain patients. Clin J Pain 1999; 15:122-131.*

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IDDS Nonmalignant Pain Patient Population

(Rauck R, Wallace M, Leong M et al. J Pain and Symptom Management. 2006;31:393-406)

- **Medical History**
  - 58% with depression
  - 25% with anxiety
  - 24% with respiratory disease
    - 6% with bronchitis
    - 7% with COPD
    - 8% with dyspnea
    - < 1% with emphysema
    - < .05% with pulmonary fibrosis diffuse interstitial
    - < .1% with decreased lung capacity
  - 14% with muscle spasms
  - 11% with back pain
  - 11% with laminectomy
  - At least 10% of patients screened reported a medical condition
- **Drug History**
  - Average of 12 oral non-opioid drugs
  - 98% (216/220) with oral opioid use (patients may have > 1 prescription)
    - 41% oxycodone + acetominophen
    - 34% oral morphine
    - 28% hydrocodone + acetominophen
    - 24% methodone
    - 18% fentanyl
    - 13% hydromorphone
  - 51% with transdermal opioids
  - 48% with parenteral opioids
  - 86% muscle relaxants
  - 62% on anxiolytics
  - 81% on antidepressants

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Databases used to Evaluate Safety of IDDS

- **MAUDE**

  FDA Disclaimer says: "MAUDE data is not intended to be used either to evaluate rates of adverse events or to compare adverse event occurrence rates across devices."
  www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfMAUDE/search.CFM

  - Voluntary reporting is incomplete
  - Limited or no drug or medical history – prevents valid analysis
  - MAUDE counts adverse events only, no total implant count for perspective
  - "Expected" mortality is unknown for this population
  - Trending can't be done reliably due to reporting changes. (Change in regulation caused a 77% increase in MDR reporting filed industry-wide in 2006 (see The Gray Sheet August 27, 2007 Vol 33 (035) p 10))

- **Medtronic Implantable System Performance Registry (ISPR)**
  - Standardized prospective data collection of real world practice
  - Long-term follow-up
  - 50 centers, 3256 pump patients for all indications (1767 non-malignant pain) with approximately 4-years follow up
    - No device related deaths
  - Pump "survival" for nonmalignant pain = Percentage of devices that remain operational
    - 36 months: 97.5%*
    - 42 months: 97.1%*

*Means 2.5% / 2.9% risk of being removed for incurring a device failure since the time of implant. (See written submission for more detailed description)

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Summary of Mortality Data for IDDS Patients

- **Medtronic Educational Brief Nov. 2006 due to cluster of spontaneous reports of deaths within 3 days of implant (or re-initiation following interrupted use) caused us to do additional investigation**
  - Cluster was purely coincidence, there was no product or drug problems, but Medtronic's investigation resulted in the communication to physicians (Educational Brief).
    - Etiology was multi-factorial – most likely caused was opioid and/or sedative drug overdose.
    - Infusion system operated normally – device malfunction was not the cause.
- **Since then Medtronic continues to monitor reports of mortality and conduct trending analysis**
  - Spontaneous reports
  - Scientific literature
  - Internal Database
- **No additional clusters of death reports since 2006**
- **Trending analysis shows that rates of death post Nov 2006-2008 are similar to those pre Nov 2006**
- **We are actively engaged on an ongoing basis with experts in the community to determine if other steps need to be taken to mitigate risks including physician communication and education, training and awareness/mitigation of patient risks**

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FDA Warning Letters and Status

Mike Baca, Medtronic Director of Quality
(Three Minutes)

- **In summer 2006 and 2007 Medtronic received two warning letters from the FDA regarding various process and product-specific issues.**
- **Areas cited**
  - **A number of quality system elements many of which were based on our system 6-7 years ago.**
  - **The design specifications change related to one specific catheter model**
  - **Pump motor stalls on one old model (Newer SynchroMed II has displaced SynchroMed EL model)**
  - **Infusion system "inflammatory mass" – a drug effect associated with intrathecal morphine**
- **FDA conducted a comprehensive re-inspection of Medtronic's quality system during June 17, 2008 – July 25, 2008. At the conclusion of the inspection, the FDA investigator reported to Medtronic that no citations or observations would be issued. (FDA Form 483)**

Field Advisories and Recalls

- **<u>SynchroMed® EL Gearshaft Wear (Motor Stalls)</u>**
  - **Safety Alert concerning a sub-set of (SynchroMed EL only) pump motors produced prior to September, 1999 that exhibited a higher than historical incidence of motor shaft wear. Engineered out of SynchroMed II.**
  - **Product has been displaced by newer SynchroMed II.**
- **<u>Product Code 8540 / 8551 Catheter Kit</u>**
  - **68 units recalled due to mis-printed product labels (Rx symbol missing).**
- **<u>Product Code 8590 Refill Kit</u>**
  - **11 units recalled due to mis-printed product labels (Rx symbol missing).**
- **<u>Inflammatory Mass (IM)</u>**
  - **The third in a series of updates to customers related to an adverse drug effect associated with intrathecal morphine. Communication provided latest rate of occurrence and updated associated technical manuals and other documentation.**
  - **Estimated occurrence: 0.49%**

Field Advisories and Recalls (cont.)

- **SynchroMed® II Missing Propellant**
  - 11,920 pumps possibly manufactured without propellant
    - Confirmed incidence 8 pumps (.06 incidence)
    - Returned to Medtronic if not implanted
    - Instructions to physicians if implanted
- **Catheters with Sutureless Connectors (Models 8709SC, 8731SC, 8596SC, 8578)**
  - Sutureless connectors were a significant improvement over the previous technology
  - Learned that physicians were not following our technical manuals and connecting them properly so we issued a Safety Alert to inform them of the problem.

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Medtronic's Commitment to Quality and Safety

- 97.5% reliability on pumps at 36 months
- Improvements to systems to drive higher quality, reliability and manufacturability to enhance effective and safe use. Recent example can be seen in SynchroMed II with redesigned motor, elimination of gear shaft issue, and improved catheter design.
- We are dedicated to continuous improvement in our products and committed to continuous communication with physicians when issues are identified.
- Therapy-related issues are much greater than the product-related issues and are addressed by Drs. Loeser and Caraway related to risk mitigations and patient access for a patient population without any other options, making this a late, if not last, resort.
  - Risks are preventable and management
  - Medtronic recognizes that there are risks associated with any interventional therapy. They must be understood within context and risk of all interventional therapies.

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Effects of IDD on Non-Malignant Pain Sufferers
Reden & Anders Analysis in Response to ECRI Questions

Scott Guillemette, Reden & Anders Lead Project Actuary
(Three Minutes)

- **Produces savings per individual per year ≈ $7,400** (PV-basis; 7/1/2006 fee levels)
  - Assumes 3% discount rate per annum
  - Assumes implantation occurs every 7 years over a 30-year time horizon from the month of implant
- **Savings are negatively correlated to the rate of re-implantation**
  - 4-year re-implantation rate ≈ $1,600 savings per individual per year
  - 6-year re-implantation rate ≈ $4,900 savings per individual per year
  - Payback period ≈ 3.7 years
- **Savings are materially derived from lower utilization in:**
  - Inpatient facility admissions (54% of total savings); and
  - Prescription drug order rates (23% of total savings)
- **Level of annual savings varies on:**
  - Duration from implantation
  - Frequency of re-implantation
  - Type of pain sufferer (i.e., Spasticity, Malignant and Non-Malignant)

PV = Present Value

Washington State Department of Labor & Industries

WA State Dept of Labor and Industries' (L&I) Experience with Implantable Drug Delivery System (IDDS) for Chronic Non-cancer Pain

Dr. Lee Glass
Associate Medical Director, L & I

August 15, 2008

Washington State Department of Labor & Industries

L&I's Experience with IDDS for Chronic Non-cancer Pain

- L&I has always covered IDDS for occupational cancer, catastrophic injury and inpatient care
- Until 2005, L&I did not cover IDDS for chronic non-cancer pain due to safety and risk/benefit concerns

	Covered?
When cancer or other end-stage disease is an accepted condition	Yes
As part of an in-patient hospitalization	Yes
During the perioperative period, not to exceed forty-eight hours from the time of discharge	Yes
When spinal cord injury is an accepted condition	Yes
For chornic, non-cancer musculoskeletal pain	No

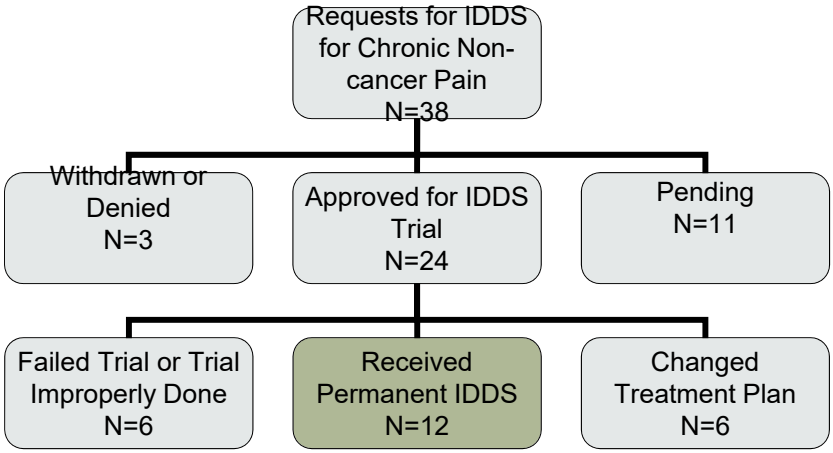
Washington State Department of Labor & Industries

L&I's Experience with IDDS for Chronic Non-cancer Pain

- In 2005, WA Court of Appeals ruled:
  - "The plain language of WAC 296-20-03014(2) excludes coverage only for certain drugs, not for their administration routes" AND
  - Worker is "...not seeking coverage for injections of opioids; rather, …seeking payment for the pump and its surgical implantation" (WAC 296-20-03002)
- Basis for ruling was a legal technicality on administrative rule rather than scientific evidence

Washington State Department of Labor & Industries

Since 2005, L&I has tracked all injured workers who have received IDDS for chronic non-cancer pain



Washington State Department of Labor & Industries

L&I's Experience with IDDS for Chronic Non-cancer Pain

- 12 workers with permanent IDDS
  - 1 worker from self-insured with insufficient data available to assess outcome
  - 11 workers from state fund
    - Average IDDS age is 26 months (12 – 74 months)
    - Type of conditions include:
      - Failed back surgery syndrome (9)
      - Chronic regional pain syndrome (1)
      - Lumbar degenerative disk disease (1)
    - 3 workers had IDDS removed

Washington State Department of Labor & Industries

	Before Implantation	At Implantation	After Implantation (As of May-June 2008)	
	Total Opioid (MED/day) Use	Initial Intrathecal Opioid	Intrathecal Opioid	Opioid (MED/day) Supplement
W1	600	Morphine 1.4mg/d	Hydromorphone 5.5mg/d + bupivacaine 3.3mg/d	37.5
W2	225	Morphine 2.7mg/d + clonidine 115.6mcg/d	Hydromorphone 1.3mg/d + bupivacaine 3.5mg/d + clonidine 231.1mcg/d	52
W3	2020	Morphine 3mg/d + bupivacaine 3.5mg/d	Hydromorphone 16mg/d + bupivacaine 3.2mg/d	576
W4	1485	Hydromorphone 4mg/d	Fentanyl 200mcg/d	1740
W5	196	Hydromorphone 0.57mg/d + bupivacaine 5.7mg/d	Hydromorphone 3.5mg/d + clonidine 30mcg/d	64
W6	7.5	Sulfentanil 3.8mcg/d	Sulfentanil 13.5mcg/d	0
W7*	120	Sulfentanil 5.76mcg/d	Sulfentanil 15.7mcg/d	300*
W8	360	Hydromorphone 1.7mg/d + bupivacaine 2.5mg/d	Hydromorphone 7.7mg/d	138
W9*	10	Hydromorphone 1.5mg/d	Hydromorphone 1.5mg/d	10*
W10	No record	No record	No record	No record
W11*	30	Sulfentanil 5.7mcg/d	Sulfentanil 9.9mcg/d	120*
W12	150	Morphine 0.5mg/d	Morphine 5.5mg/d	150
Average	**473**			**345**

MED = Morphine Equivalent Dose

***IT pump removed & opioid supplement dose at time of removal**

Washington State Department of Labor & Industries

	Before Implantation		After Implantation (As of May-June 2008)		
	Pain (VAS)	Function	Pain (VAS)	Function	Work Status
W1	7.5	Not reported	Not reported	Not reported	Not working / timeloss
W2	8.5	Not reported	Not reported	Not reported	Not working / timeloss
W3	7.5	Not reported	6.5	Not reported	Not working / timeloss
W4	5	Walk 45 min x 2/week	7	Not reported	Not working / timeloss
W5	4	Not reported	9	Not reported	Not working / timeloss
W6	8.5	Reduced activity of daily living	7	Not reported	Not working / timeloss
W7*	7	Stand<15 min	7*	Minimal progress in PT*	Not working / timeloss
W8	9.5	Neck disability index>35	8	"do more stuff around the house"	Not working / timeloss
W9*	7	Not reported	5*	Not reported*	Not working / timeloss
W10	No record	No record	No record	No record	No record
W11*	6	Not reported	8.5*	Not reported*	Not working / timeloss
W12	3	Can do activity of daily living	4	Can do activity of daily living	Not working / timeloss
Average	**6.7**		**6.9**		

VAS = Visual Analogue Scale

***IT pump removed & VAS/Function at time of removal**

Washington State Department of Labor & Industries

Side-effects Reported by Providers

W1	
W2	Tiredness, difficulty thinking, testosterone deficiency, xerostomia, erectile dysfunction, lymphedema
W3	
W4	Lymphedema, "narcolepsy"
W5	Testosterone deficiency, sleep apnea, lymphedema, erectile dysfunction
W6	
W7*	CSF leak after pump removal
W8	Testosterone deficiency, erectile dysfunction
W9*	
W10	No record
W11*	Mild wound infection 5 days post-op, recurrent post-dural puncture headaches
W12	

***IT pump removed**

Washington State Department of Labor & Industries

L&I's Experience with IDDS for Chronic Non-cancer Pain

Summary:

- 10 of 11 workers using drug(s) not FDA approved for intrathecal administration
- 3 of 11 workers currently are receiving intrathecal dose(s) above the Polyanalgesic Consensus recommendation for maximum dose/day*
- 10 of 11 workers require on-going opioids (oral or transdermal) in addition to their intrathecal opioid dose
  - 5 workers taking same or higher oral/transdermal opioid dose than they were before pump implantation

*Deer T, Krames ES, Hassenbusch SJ, Burton A, Caraway D, Dupen S, et al. Polyanalgesic Consensus Conference 2007: Recommendations for the Management of Pain by Intrathecal (Intraspinal) Drug Delivery: Report of an Interdisciplinary Expert Panel. Neuromodulation 2007;10 (4):300-328.

Washington State Department of Labor & Industries

L&I's Experience with IDDS for Chronic Non-cancer Pain

Summary continued:

- 6 of 11 workers have reported side-effects, many serious
- 9 of 11 workers have documented pre/post VAS scores
  - 4 workers have improved self-reported pain
    - 1 worker had a 29% reduction
    - 3 workers have between 13% - 18% reduction
  - 5 workers have same or higher pain levels
- Function was reported in 3 of 11 workers
- 11 workers currently receiving time-loss (unable to work)

Washington State Department of Labor & Industries

L&I's Experience with IDDS for Chronic Non-cancer Pain

Conclusions:

- L&I's experience overall shows little reported benefit in pain and function or reduction in opioid supplement
- Serious side-effects reported
- Benefits do not outweigh risks for workers with chronic non-cancer pain

Washington State Health Care Authority

State Agency Experience
IDDS Pumps for
Chronic Non-Cancer Pain
August 15, 2008

Health Technology Assessment
676 Woodland Square Loop SE
PO Box 42712
Olympia, WA 98504-2712
Phone 360-923-2742.
www.hta.hca.wa.gov

Agency Experience & Background

CNCP (Chronic non-cancer pain) is an important and common medical concern worldwide. The International Association for Study of Pain (IASP) defines chronic pain as pain lasting beyond the normal time of healing, defined as three months or longer.

The most common source is low back pain. Prevalence rates of chronic pain (any severity) to be as high as 55% and an estimated 9% of Americans have moderate to severe CNCP (ECRI Review). Most find adequate relief from conservative therapy or treatment of underlying/co-morbid condition (ECRI Review). Estimated 1% to 20% have pain resistant to treatment or unacceptable side effects ((Williams et al. INHATA Review,

Medical management and conservative pain relief therapies with good evidence of moderate efficacy for chronic or subacute low back pain are cognitive-behavioral therapy, exercise, spinal manipulation, and interdisciplinary rehabilitation. For acute low back pain, a therapy with good evidence of efficacy is superficial heat. Although conservative and surgical therapy may provide adequate care for most CNCP patients, in some patients even exhaustive use of these methods fails due to insufficient pain relief or unacceptable adverse events. Patients with pain resistant to all conventional therapies may be candidates for an implantable drug delivery system (IDDS).

IDDS is a device which is fully surgically implanted into the patient to provide round-the clock long-term drug therapy. In a surgical procedure, the pump itself is implanted, usually in the abdomen, and a catheter is tunneled to the site of drug delivery. Because medications are delivered directly to the desired site, pain control is theoretically optimized while adverse events associated with systemic administration are theoretically minimized because the overall drug dose is reduced

IDDS pumps have been implanted for the treatment of chronic non-cancer pain (e.g., failed back surgery, syndrome (FBSS)), peripheral vascular disease, and osteoporosis. The agencies are requesting a review for the use of IDDS pumps for **chronic non-cancer pain only.**

Potential Benefits that an IDDS may have are:

- Lower dose and effective pain relief by delivery of opioids direct to spinal cord (instead of systemic oral/injected)
- Fewer side effects due to lower dose/direct administration
- Better pain control leads to:
    - Improved quality of life
    - Improved functional status
    - Improved employment status
- Reduced addiction/tolerance
- Patient convenience

Potential drawbacks:

- IDDS treatment is invasive, prone to side-effects and complications, costly, and requires a large amount of technical support (Williams et al. INHATA Review, 2000)
- Safety Issues

  - Overdose of infused medications
  - Infused drug side effects
  - Device/ Mechanical pump complications
  - Surgical Complications
- Invasive procedure that is an additional method to deliver opioids (not replacement or different treatment mechanism for individuals with chronic pain)
- Tolerance and dose escalation of infused and adjudavent oral medications
- Permanent implantation implications
  - Non-life threatening condition with unknown resolution
  - Generally middle age candidates
  - Maintenance and revisions required –risks with each surgery; long term patient and provider commitment
- Costs and specialty provider availability for long term

The key concerns and prioritization information are listed below. The primary concern is around safety.

- **Safety concern: High**
  - Drug tolerance and drug-related side effects
  - Device related complications
  - Multiple follow-up services
  - Overdose and surgical complications
- **Efficacy concern: Medium**
  - Many patients still experience chronic moderate to severe pain even with implant.
  - No improvement in disability or employment status
  - Removal rate for intolerance or lack of effect
- **Cost Concern: Low**
  - Individual cost for technology is relatively high, but implantation for chronic pain utilization is currently very low.
  - However, current utilization/dissemination may change if widely permitted and
  - population with chronic pain is significant

State Agency IDDS Medical Coverage Policy

All Washington agencies cover IDDS pumps without restrictions for:

- Cancer Pain
- Chemotherapy
- Spasticity

IDDS pumps for chronic non-cancer pain

- Historically covered in DSHS and HCA
- Recently covered at L&I, with protocols, due to litigation

The technology review is for the use of IDDS pumps for **chronic non-cancer pain only**

- Other uses of IDDS will not be impacted by HTCC decision

State Agency Utilization

Monitoring cost changes in health expenditures is fundamental to sound policymaking. The agencies use this information to assess the potential impact of new proposals and evaluate current programs. The agencies continually refine what is collected, analyzed and reported in order to provide current, relevant information in a changing health care world. The decisions that the state agencies make have impacts throughout the state. When combined, the participating state agencies are responsible for medical services for over 750,000 people in the state of Washington.

Approximate population affected by HTCC coverage decisions

State Agencies	Affected Population
Uniform Medical Plan	173,000
Labor and Industries	150,000
Medicaid	450,000

To measure the impact of the committee's decision regarding IDDS for chronic non-cancer pain, the agencies have provided population and cost information to provide a state utilization picture. However, utilization information is not complete because:

- Billings include secondary payments.
- Limited eligibility.
- Patients are still in the process of receiving medical services.

IDDS Pumps (all diagnoses)

The following table outlines participating state agency utilization for IDDS pumps surgical services from SFY 2002 – SFY 2008. This includes chemotherapy, spasticity, chronic cancer pain and chronic non-cancer pain patients.

IDDS Procedure	Patients	Total Cost
Implantation (all diagnoses)	324	$5.2 Million

***Pump surgical costs include 3 +/- days from surgery date.**

IDDS Pumps for Chronic Non-Cancer Pain

Screening, Implantation, Revision and Removal

IDDS for CNCP seeks to replace the route of opioid administration to achieve better pain control with fewer adverse effects (Williams et al. INHATA Review, 2000). The first step toward implantation is to have a screening, also referred to as a trial.

Trials allow physicians and patients to review whether IDDS implantation will provide them with acceptable pain relief. These trials typically include the fitting of a catheter attached to an external pump to infuse the appropriate pain relieving drugs. Trials can last from several days to several weeks. Although protocol outlines the need for a trial for patient safety and review of patient satisfaction before implantation, not all of the patients identified in the administrative claims data had this screening. This could be due to eligibility changes during medical services.

IDDS treatment is invasive, prone to side-effects and complications, costly, and requires a large amount of technical support (Williams et al. INHATA Review, 2000). The below table outlines the participating agencies' utilization for IDDS pumps surgical services for chronic non-cancer pain from SFY 2002 – present.

IDDS Procedure	Patient Count – All Agency	Average Cost per Patient	Cost Range
Implantation (CNCP Only)	93	$12,664	$10,268 - $15,060
*Screening/Trials	37	$12,118	$11,808 - $15,472
Removal	15	$11,898	$10,972 – $12,823

Costs included +/- 3 days from occurrence. L&I data is not complete.

Maintenance and Injectable Drugs

In reviewing the participating state agencies' utilization information, it was noted that there were few billings outlining the type of drug (s) used within the IDDS pumps to provide pain relief. The table below outlines maintenance (e.g., analysis and refillings) and the small amount of infused drugs found within the administrative claims data since 2002.

Service	Average Cost per Patient per Refill	Units Billed	Total Cost
Maintenance and injected IDDS drugs (e.g., refills, analysis)	$238	360	$99,530

Maintenance occurred every 6 – 8 weeks.

Pharmaceuticals

Pharmaceuticals (oral drugs) are also used for pain control. The administrative claims data was searched for the following pain categories: anticonvulsant, opioid, antidepressant, muscle relaxants and anti-inflammatory. The utilization below outlines pharmaceuticals billed in the last **quarter** of eligibility after IDDS implantation.

Service	Service Number	Total Cost
Pharmacy (oral medications) last quarter	32	$16,301

Clinical Treatment Guidelines

Organization	Date	Outcome	Evidence Cited?
American Society of Interventional Pain Physicians (Boswell et. al)	2007	"Evidence for implantable intrathecal infusion systems is strong for short term improvement in pain of malignant or neuropathic pain. The evidence is moderate for long term management of chronic pain."	Y
Sisken Hospital for Physical Rehabilitation (Sanders et. al)	2005	"Studies and systematic reviews regarding the efficacy of infusion pumps and spinal cord stimulators have increased. Thus far, they have not met the current criteria for adequate supportive evidence to recommend the application to CPS (chronic pain syndrome) patients".	Y
International Research Foundation for RSD/CRPS (Kirkpatirck et. al)	2003	No conclusion offered, however authoirs note that "morphine pumps" have not been clinically shown to be superior to oral morphine.	Not reported

MEDICARE COVERAGE DECISION

A. General

Infusion pumps are medical devices used to deliver solutions containing parenteral drugs under pressure at a regulated flow rate.

Indications and Limitations of Coverage

B. Nationally Covered Indications

The following indications for treatment using infusion pumps are covered under Medicare:

1. External Infusion Pumps
    a. Iron Poisoning (Effective for Services Performed On or After September 26, 1984)

       When used in the administration of deferoxamine for the treatment of acute iron poisoning and iron overload, only external infusion pumps are covered.
    b. Thromboembolic Disease (Effective for Services Performed On or After September 26, 1984)

       When used in the administration of heparin for the treatment of thromboembolic disease and/or pulmonary embolism, only external infusion pumps used in an institutional setting are covered.
    c. Chemotherapy for Liver Cancer (Effective for Services Performed On or After January 29, 1985)

       The external chemotherapy infusion pump is covered when used in the treatment of primary hepatocellular carcinoma or colorectal cancer where this disease is unresectable; OR, where the patient refuses surgical excision of the tumor.

d. Morphine for Intractable Cancer Pain (Effective for Services Performed On or After April 22, 1985)

Morphine infusion via an external infusion pump is covered when used in the treatment of intractable pain caused by cancer (in either an inpatient or outpatient setting, including a hospice).

e. Continuous Subcutaneous Insulin Infusion (CSII) Pumps (Effective for Services Performed On or after December 17, 2004)

Continuous subcutaneous insulin infusion (CSII) and related drugs/supplies are covered as medically reasonable and necessary in the home setting for the treatment of diabetic patients who: (1) either meet the updated fasting C-Peptide testing requirement, or, are beta cell autoantibody positive; and, (2) satisfy the remaining criteria for insulin pump therapy as described below. Patients must meet either Criterion A or B as follows:

Criterion A: The patient has completed a comprehensive diabetes education program, and has been on a program of multiple daily injections of insulin (i.e., at least 3 injections per day), with frequent self-adjustments of insulin doses for at least 6 months prior to initiation of the insulin pump, and has documented frequency of glucose self-testing an average of at least 4 times per day during the 2 months prior to initiation of the insulin pump, and meets one or more of the following criteria while on the multiple daily injection regimen:

- Glycosylated hemoglobin level (HbAlc) > 7.0 percent;
- History of recurring hypoglycemia;
- Wide fluctuations in blood glucose before mealtime;
- Dawn phenomenon with fasting blood sugars frequently exceeding 200 mg/dl; or,
- History of severe glycemic excursions.

Criterion B: The patient with diabetes has been on a pump prior to enrollment in Medicare and has documented frequency of glucose self-testing an average of at least 4 times per day during the month prior to Medicare enrollment.

General CSII Criteria

In addition to meeting Criterion A or B above, the following general requirements must be met:

The patient with diabetes must be insulinopenic per the updated fasting C-peptide testing requirement, or, as an alternative, must be beta cell autoantibody positive.

Updated fasting C-peptide testing requirement:

- Insulinopenia is defined as a fasting C-peptide level that is less than or equal to 110% of the lower limit of normal of the laboratory's measurement method.
- For patients with renal insufficiency and creatinine clearance (actual or calculated from age, gender, weight, and serum creatinine) <50 ml/minute, insulinopenia is defined as a fasting C-peptide level that is less than or equal to 200% of the lower limit of normal of the laboratory's measurement method.
- Fasting C-peptide levels will only be considered valid with a concurrently obtained fasting glucose <225 mg/dL.
- Levels only need to be documented once in the medical records.

Continued coverage of the insulin pump would require that the patient be seen and evaluated by the treating physician at least every 3 months.

The pump must be ordered by and follow-up care of the patient must be managed by a physician who manages multiple patients with CSII and who works closely with a team including nurses, diabetes educators, and dietitians who are knowledgeable in the use of CSII.

Other Uses of CSII

The CMS will continue to allow coverage of all other uses of CSII in accordance with the Category B investigational device exemption (IDE) clinical trials regulation (42 CFR 405.201) or as a routine cost under the clinical trials policy (Medicare National Coverage Determinations (NCD) Manual 310.1).

f. Other Uses

Other uses of external infusion pumps are covered if the contractor's medical staff verifies the appropriateness of the therapy and the prescribed pump for the individual patient. (see TN 242)

NOTE: Payment may also be made for drugs necessary for the effective use of a covered external infusion pump as long as the drug being used with the pump is itself reasonable and necessary for the patient's treatment.

2. Implantable Infusion Pumps

a. Chemotherapy for Liver Cancer (Effective for Services Performed On or After September 26, 1984)

The implantable infusion pump is covered for intra-arterial infusion of 5-FUdR for the treatment of liver cancer for patients with primary hepatocellular carcinoma or Duke's Class D colorectal cancer, in whom the metastases are limited to the liver, and where: (1) the disease is unresectable, or (2) the patient refuses surgical excision of the tumor.

b. Anti-Spasmodic Drugs for Severe Spasticity

An implantable infusion pump is covered when used to administer anti-spasmodic drugs intrathecally (e.g., baclofen) to treat chronic intractable spasticity in patients who have proven unresponsive to less invasive medical therapy as determined by the following criteria:

As indicated by at least a 6-week trial, the patient cannot be maintained on noninvasive methods of spasm control, such as oral anti-spasmodic drugs, either because these methods fail to control adequately the spasticity or produce intolerable side effects, and prior to pump implantation, the patient must have responded favorably to a trial intrathecal dose of the anti-spasmodic drug.

c. Opioid Drugs for Treatment of Chronic Intractable Pain

An implantable infusion pump is covered when used to administer opioid drugs (e.g., morphine) intrathecally or epidurally for treatment of severe chronic intractable pain of malignant or nonmalignant origin in patients who have a life expectancy of at least 3 months, and who have proven unresponsive to less invasive medical therapy as determined by the following criteria:

The patient's history must indicate that he/she would not respond adequately to noninvasive methods of pain control, such as systemic opioids (including attempts to eliminate physical and behavioral abnormalities which may cause an exaggerated reaction to pain); and a preliminary trial of intraspinal opioid drug administration must be undertaken with a temporary intrathecal/epidural catheter to substantiate adequately acceptable pain relief and degree of side effects (including effects on the activities of daily living) and patient acceptance.

d. Coverage of Other Uses of Implanted Infusion Pumps

Determinations may be made on coverage of other uses of implanted infusion pumps if the contractor's medical staff verifies that:

- The drug is reasonable and necessary for the treatment of the individual patient;
- It is medically necessary that the drug be administered by an implanted infusion pump; and,
- The Food and Drug Administration (FDA)-approved labeling for the pump must specify that the drug being administered and the purpose for which it is administered is an indicated use for the pump.

e. Implantation of Infusion Pump Is Contraindicated

The implantation of an infusion pump is contraindicated in the following patients:

- With a known allergy or hypersensitivity to the drug being used (e.g., oral baclofen, morphine, etc.);
- Who have an infection;
- Whose body size is insufficient to support the weight and bulk of the device; and,
- With other implanted programmable devices since crosstalk between devices may inadvertently change the prescription.

NOTE: Payment may also be made for drugs necessary for the effective use of an implantable infusion pump as long as the drug being used with the pump is itself reasonable and necessary for the patient's treatment.

C. Nationally Noncovered Indications

The following indications for treatment using infusion pumps are not covered under Medicare:

1. External Infusion Pumps
   a. Vancomycin (Effective for Services Beginning On or After September 1, 1996)

      Medicare coverage of vancomycin as a durable medical equipment infusion pump benefit is not covered. There is insufficient evidence to support the necessity of using an external infusion pump, instead of a disposable elastomeric pump or the gravity drip method, to administer vancomycin in a safe and appropriate manner.

2. Implantable Infusion Pump
   a. Thromboembolic Disease (Effective for Services Performed On or After September 26, 1984)

      According to the Public Health Service, there is insufficient published clinical data to support the safety and effectiveness of the heparin implantable pump. Therefore, the use of an implantable infusion pump for infusion of heparin in the treatment of recurrent thromboembolic disease is not covered.

   b. Diabetes

      An implanted infusion pump for the infusion of insulin to treat diabetes is not covered. The data does not demonstrate that the pump provides effective administration of insulin.

D. Other

Not applicable.

(This NCD last reviewed January 2005.)

Implanted Infusion Pumps for Chronic Noncancer Pain

Health Technology Clinical Committee Meeting
Washington State Health Technology Assessment Program

Meredith Noble, M.S.
Jonathan R. Treadwell, Ph.D.
Karen Schoelles, M.D., S.M.

Seattle, Washington
August 15, 2008

ECRI Institute
The Discipline of Science. The Integrity of Independence.

Chronic Noncancer Pain (CNCP)

- Pain lasting three months or longer (International Association for the Study of Pain)
- Older individuals, women, and people with certain diseases are more likely to suffer from chronic pain
- Variety of causes, most common cause back pain

ECRI Institute
The Discipline of Science. The Integrity of Independence.

Conservative Therapies

- Simple analgesics, co-analgesics, opioids and opioid compound analgesics
- Physical therapy and massage therapy
- Steroid injections, trigger point injections
- Acupuncture
- Cognitive behavioral therapy
- Correction of underlying disorder when possible

ECRI Institute
The Discipline of Science. The Integrity of Independence.

Potential Candidates for Implanted Infusion Pumps for Pain Therapy

- For whom conservative treatments have failed and available options have been exhausted
- Are ineligible for corrective surgery
- Need round-the-clock, constant pain control
- May be required to pass a psychological evaluation

ECRI Institute
The Discipline of Science. The Integrity of Independence.

Implantable Infusion Pumps

- Pumps are surgically implanted under the skin.
- A catheter delivers drugs from the pump to the intended site of delivery (e.g. intravenous, intraarterial, subcutaneous, intraperitoneal, intrathecal, epidural, or intraventricular site)
- Some pumps are programmable
- Pump reservoir can be refilled as needed

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Drugs Used

- Morphine sulfate appears to be most commonly used and is approved by the FDA for intrathecal use
- Other opioids (including hydromorphone, methadone, sufentanil) and anesthetics (e.g. bupivacaine) or other drugs (e.g. clonidine) were used off-label in studies we identified
- Ziconotide is calcium channel blocker approved by the FDA for intrathecal use when morphine fails

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Theoretical Benefits

- Pain control when other methods have failed
- Bypass of systemic administration reduces dose needed and adverse drug events/effects
- Convenient for patient
- Minimizes risk of abuse and diversion of opioids

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Possible Risks

- Surgical complications
- Device failure
- Drug complications
- Lack of effectiveness

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Key Questions

1. What is the evidence for efficacy and effectiveness of implantable infusion pumps?
2. What is the safety profile of implantable infusion pumps?
3. Is there any evidence of differential efficacy or safety issues amongst special populations?
4. What are the cost implications and cost effectiveness for implantable infusion pumps?

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Study Inclusion Criteria: General

- English-language, full-length articles reporting at least one outcome of interest and no duplicate data on at least 10 individuals with IASP-defined chronic pain due to noncancer causes

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Study Inclusion Criteria: Effectiveness

- Clinical studies must be either prospective or retrospective with consecutive enrollment or randomized selection of patients
- Patients were treated for at least six months
- Outcomes must not have required patients to remember earlier health states
- Instruments accepted for reliability in published literature

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Study Inclusion Criteria: Cost Issues

- Any original relevant cost analysis or cost effectiveness analysis

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Literature Search Results

- 549 abstracts identified, 88 retrieved
- 16 included
  - 13 case series on intrathecal drug administration
  - 4 cost analyses
  - 1 study was both a case series and cost analysis

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Case Series

- No control group means less certainty that the observed effect is entirely due to the intervention in question
- A rigorous Cochrane review has suggested that placebo response in pain patients is relatively small
- Natural history of pain in pump candidates is stable and unremitting despite exhaustive attempts at conservative treatment

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Methods of Analysis

- We use meta-analysis within a formal framework to summarize evidence
- This does not necessarily mean that every outcome will have a quantitative conclusion (in this report, most did not)

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Using Meta-Analysis

- Increasing the power
- Transparent methodology for drawing conclusions (or deciding not to)
- Formal, objective framework that can be used to investigate potential reasons for different findings across studies
- Formal, objective methods to evaluate the consistency and robustness of conclusions.

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Using Meta-Analysis

- Avoiding vote counting methods in which the qualitative findings of each study in the evidence base are:
  - Considered side-by-side but never pooled quantitatively or weighted objectively, possibly leading to errors
  - Subjectivity in assessing relationships between outcomes and potential moderator variables
- Vote counting has been recommended as a method of "last resort," only to be performed when effect sizes and significance levels of the studies are unavailable.

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ECRI Institute Rating of Conclusions

- System is objective, determined *a priori*, and based upon:
  - Internal validity (quality)
  - Quantity
  - Consistency
  - Robustness
- System distinguishes qualitative and quantitative conclusions

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Findings

Effectiveness and Safety

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Evidence Base:

Effectiveness and Safety: Enrollment Criteria

- 13 case series
- Chronic noncancer pain
- Conservative treatment methods failed
- Not eligible for corrective surgery
- Eight stated that they screened out candidates for psychological reasons
- Eight stated that only the candidates with successful trials received a pump

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Evidence Base:

Effectiveness and Safety: Patient Characteristics

- 413 patients (range 11-30 per study)
- Severe pain: Pooled baseline pain score 8.7 (SD 2.7) out of 10
- Primary pain conditions:
  - Various or unspecified pain types (6 studies)
  - Failed back surgery syndrome (4 studies)
  - Low back pain due to any etiology (1 study)
  - Osteoporotic vertebral fracture (1 study)
  - Neuropathic pain (1 study)

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Evidence Base:

Effectiveness and Safety: Patient Characteristics

- Patients highly selected
- Mean duration of pain 19 months, 6.8 years, 8 years (two studies), and 9.5 years
- Most studies reported mean ages in the mid-forties to mid-fifties.
- In most studies more women enrolled than men.

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Evidence Base:

Effectiveness and Safety: Study Protocols

- 8 prospective, 3 retrospective, 2 unclear
- 3 studies did not screen all patients with trial
- Pumps were mostly programmable
- Most allowed adjuvant and rescue medications
- Duration of treatment 6 months to 3 years

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Evidence Base:

Effectiveness and Safety: Study Protocols

- Morphine
  - Alternatives sufentanil (1 study), fentanyl (1 study) or hydromorphone, fentanyl, and/or methadone (1 study)
  - Adjuvant infused drugs clonidine (1 study), bupivacaine (1 study), tetracaine or bupivacaine (1 study), bupivacaine, clonidine, or midazolam (1 study), or clonidine, baclofen, or bupivacaine (1 study)
- Methadone (1 study)
- Not reported (1 study)

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Evidence Base:

Effectiveness and Safety: Internal Validity

- Evaluated for each study for each outcome
- Threats to internal validity included
  - Failure to compare characteristics at baseline and follow-up when attrition occurred
  - Retrospective study design
  - Use of ancillary treatments
  - Some outcomes subjective
  - Funding from a source with interest in the outcome
- Low internal validity ratings

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Key Question 1

- What is the evidence of efficacy and effectiveness of implantable infusion pumps?

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KQ1: Pain (Continuous)

Study	Number (%) evaluated and enrolled	Mean (SD) Baseline pain score	Mean (SD) Follow-up pain score	Duration of treatment
Shaladi et al. 2007	24 (100%) / 24	8.7 (0.5)	1.9 (1.0)	12 months
Anderson et al. 2003	24 (89%) / 27	8.12 (1.02)	3.93 (2.10)	6 months
Kumar et al. 2001	16 (100%) /16	9.18 (0.28)	3.42 (1.32)	29 months mean
Mironer and Tollison 2001	24 (100%) / 24	8.5 (1.1)	5.8 (3.2)	6 months
Rainov et al. 2001	26 (100%) / 26	8.2 (3.8)	4.1 (3.5)	27 months mean
Angel et al. 1998	11 (100%) / 11	9.5 (0.4)	5.2 (3.0)	27 months mean
Hassenbusch et al. 1995	18 (100%) / 18	8.5 (0.92)	6.2 (1.8)	29 months mean
All 7 Studies	**143 (98%) / 146**	**8.7 (2.7)**	**3.5 (1.99) to 4.3 (0.72)**	Range 6 months to 29 months

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KQ1: Pain (Continuous)

- **Drug infusion with an implantable infusion pumps leads to clinically significant pain relief in patients with CNCP**
- **Strength of evidence: weak**

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KQ1: Pain (Dichotomous)
At least 25% Relief

Study	Number (%) with ≥25% Relief	Number enrolled	Duration of Treatment
Hassenbusch et al. 1995	11 (61%)	18	29 months mean
Angel et al. 1998	7 (64%)	11	27 months mean
Anderson and Burchiel 1999	11 (37%)	30	24 months
Kumar et al. 2001	12 (75%)	16	29 months mean
Mironer and Tollison 2001	11 (45%)	24	6 months
Shaladi et al. 2007	24 (100%)	24	12 months
All 6 studies with 123 patients	**60.4% (95% CI 42.1%-76.2%)**		Range 6 months to 29 months mean

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KQ1: Pain (Dichotomous)
At least 50% Relief

Study	Number (%) with ≥50% Relief	Number enrolled	Duration of Treatment
Hassenbusch et al. 1995	2 (11%)	18	29 months mean
Angel et al. 1998	7 (64%)	11	27 months mean
Anderson and Burchiel 1999	8 (29%)	30	24 months
Kumar et al. 2001	7 (44%)	16	29 months mean
Mironer and Tollison 2001	9 (38%)	24	6 months
Anderson et al. 2003	15 (63%)	27	6 months
Shaladi et al. 2007	24 (100%)	24	12 months
All 7 studies with 150 patients	**40.8% (95% CI 25.2% - 58.5%)**		Range 6 months to 29 months mean

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KQ1: Discontinuation from Trial due to Insufficient Pain Relief

Study	Number (%) that discontinued	Number enrolled	Duration of treatment
Hassenbusch et al. 1995	2 (11%)	18	29 months mean
Angel et al. 1998	1 (9.1%)	11	27 months mean
Anderson and Burchiel 1999	1 (3.3%)	30	24 months
Kumar et al. 2001	2 (12.5%)	16	29 months mean
Anderson et al. 2003	1 (3.7%)	27	6 months
All 5 studies with 102 patients	**8.0% (95% CI 3.8% - 15.8%)**		6 to mean 29 months

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KQ1: Discontinuation from Trial due to Insufficient Pain Relief

- **Of patients who began treatment with an implantable pump used for intrathecal opioid delivery for CNCP, 8.0% (95% 3.8%-15.8%) discontinued treatment in the clinical trial due to insufficient pain relief.**
- **Stability of evidence: Low**

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KQ1: Other Medications and Treatments

- Reasons for use of other medications and treatments besides effectiveness of intrathecal drugs
  - Clinical study protocols
  - Other indications
- Therefore, we did not attempt to rate the strength or stability of the evidence

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KQ1: Quality of Life

Scale	Study	BL Mean (SD)	FU Mean (SD)	N (%)	Longest FU Time	SMD (95% CI)	P=
Tollison QOL Scale	Mironer and Tollison 2001	66.9 (20.4)	63.1 (23.2)	24 (100%)	6 mo	0.170 (-0.232-0.573)	0.409
Questionnaire of the European Foundation of Osteoporosis (QUALEFFO)	Shaladi et al. 2007	114.8 (10.4)	79.1 (13.4)	24 (100%)	12 mo	2.91 (1.99-3.92)	<0.001

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KQ 1: Functional Status

Study	Scale	BL Mean (SD)	FU Mean (SD)	N (%)	SMD (95% CI)	P=
Anderson et al. 2003	Short-form Sickness Impact Profile (s-SIP)	14.8 (4.3)	9.1 (5.4)	24 (100%)	1.15 (0.637-1.669)	<0.001

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KQ1: Employment Status

Study	N= Enrolled	N= (%) working / N=eligible at BL	N= (%) working / N=eligible at FU	OR (95%CI)	P=
Kanoff 1994	15	0/15 (0%)	6/15 (40%)	21.21 (1.79-251.56)	0.015
Tutak & Doleys 1996	26	5/26 (19%)	6/26 (23%)	1.26 (0.49-3.24)	0.632
Anderson & Burchiel 1999	30	16/30 (36%)	13/20 (65%)	1.62 (0.84-6.48)	0.250
Thimineur et al. 2004	44	1/22 (5%)	3/22 (14%)	3.32 (0.03-4.86)	0.180
All 4 studies	**115**	**83/93 (89%) for evaluation**		**2.12 (0.941-4.767)**	**0.070**

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No conclusions possible for:

- Quality of life
  - Insufficient quantity of evidence
- Function
  - Insufficient quantity of evidence
- Change in employment
  - Inconsistent evidence

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KQ1: Other Medications and Treatments

- Nine studies with 347 patients
- Due to differences in reporting among the studies, their findings could not be pooled or otherwise quantitatively summarized
- Despite differences in measurement and reporting, all studies reported a decrease in the number of patients using other treatments and/or a decrease in the quantity of medications used

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KQ1: Other Medications and Treatments

- **Intrathecal administration of opioids by implantable pump was associated with an overall decrease in the quantity of other drugs taken or a decrease in the proportion of patients taking other drugs.**

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KQ1: Changes in Quantity of Infused Medication Administered

- Reasons for change in quantity of infused medication administered besides effectiveness:
  - Titration
  - Differences in prescribing preferences
  - Progression of underlying disease
  - Unclear causal relationship between pain levels and quantities of medication
- Therefore, we did not attempt to rate the strength or stability of the evidence

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KQ1: Changes in Quantity of Infused Medication Administered

- **The dose of medication infused by an implanted infusion pump increased over time, but the amount of dose change is not predictable from available studies**

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Key Question 2

- What is the safety profile of implanted infusion pumps?

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KQ2: Discontinuation from Clinical Study due to Adverse Events

Study	N= Enrolled	N= Discontinued	Percentage that discontinued (95% CI)
Krames & Lanning 1993	16	2	12.5% (3.1%-38.6%)
Kanoff 1994	15	1	6.7% (0.9%-35.2%)
Hassenbusch 1995	18	0	2.6% (0.02-31.0%)
Tutak & Doleys 1996	26	1	3.8% (0.5%-22.8%)
Angel 1998	11	2	18.2% (4.6%-50.7%)
Anderson & Burchiel 1999	30	1	3.3% (0.5%-20.2%)
Kumar 2001	16	2	12.5% (3.1%-38.6%)
All 7 studies	**132**	**8.3% (4.4%-15.1%)**	

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KQ2: Discontinuation from Clinical Study due to Adverse Events

- **Of patients with chronic noncancer pain who begin intrathecal opioid therapy with an implanted pump, 8.3% (95% CI 4.4%-15.1%) of patients discontinued treatment in the clinical study due to adverse events and effects.**
- **Stability of estimate: Low**

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KQ 2: Adverse Events (Case Series)

- Variability of reporting
  - Methods for reporting events observed
  - Failure to report absence of unobserved AEs
  - Inconsistent use of definitions and methods of reporting across studies
- Reporting incomplete
  - Severity
  - Duration
  - Treatability
- Precluded pooling of data

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KQ 2: Adverse Events (Case Series)

- Most common opioid-related AEs
  - Gastrointestinal (Constipation, nausea, dyspepsia)
  - Headache
  - Fatigue/lethargy/somnolence
  - Urinary (retention, hesitancy, “disturbance”)
- No life-threatening drug-related adverse events were reported

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KQ 2: Adverse Events (Case Series)

- Device-Related Adverse Events
  - Malfunctions
  - Malpositioning
  - Surgical and post-surgical complications
- Percentage of patients who required re-operation ranged from 9% to 42%

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KQ 2: Adverse Events (Case Series)

- 7 deaths in 3 studies
  - 2 Myocardial infarctions
  - 1 Death during surgery for elective coronary angioplasty
  - 1 Chronic obstructive pulmonary disease
  - 1 Pericolonic abscess
  - 1 Suicide
  - 1 Unknown causes

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KQ2: Adverse Events (MAUDE)

- FDA Manufacturer and User Facility Device Experience Database
- Limitations
  - Total number of implanted infusion pumps unknown
  - Not possible to limit indications to chronic noncancer pain
  - Severity, duration, and treatability of event generally not reported
  - Not always possible to definitively attribute event to pump or drug
  - Voluntary

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KQ2: Adverse Events (MAUDE)

- Unfiltered search of implantable pump product (ProCode LKK) 1996 though mid-2007 yields 9,082 reports
  - 343 Deaths
  - 3,817 Serious injuries
  - 2,692 Malfunctions
  - 2,174 Other
  - 56 Invalid Data

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KQ2: Adverse Events (MAUDE)

- Filtered search refined with key words related to treatment of chronic noncancer pain
- Eliminated some adverse event reports for use of implanted infusion pumps from purposes other than treatment of chronic pain (e.g. insulin pumps). This does not eliminate reports for treatment of cancer pain or spasticity.

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KQ2: Adverse Events (MAUDE)

- 975 potentially relevant reports were identified
- We divided by
  - Deaths
  - Health outcome (possibly drug-related)
  - Device-related

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KQ2: Adverse Events (MAUDE)

- 53 deaths
  - Unknown causes (15 reports)
  - Cardio/Pulmonary arrest (7 reports)
  - Cardiac disease (5 reports)
  - Drug overdose (5 reports)

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KQ2: Adverse Events (MAUDE)

- Serious and potentially serious reports
  - Infection (128 reports)
  - Inflammatory mass(es) (83 reports)
  - Respiratory difficulty (28 reports)
  - Paralysis (20 reports)

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KQ2: Adverse Events (MAUDE)

- Device-related
  - Re-operation due to pump or catheter failure (405 reports)
  - Removal of pump without replacement (211 reports)
  - Non-operative equipment revision (86 reports)
  - Operator error (35 reports)

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KQ2: Additional Information

- Early Mortality
  - 9 patients died within 3 days of pump implantation between 12/2005 and 3/2006
  - Attributed by Medtronic to user error
- Endocrine Effects
  - Decreased libido, hypogonadism, amenorrhea, impotence
  - High prevalence in some long-term retrospective clinical studies

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KQ2: Additional Information

- Granuloma
  - Inflammatory masses at or near distal tip of catheter that cause pain and catheter occlusion
  - Medtronic estimates incidence of 0.49%
- Catheter Connection Failure
  - Improper sutureless connector (SC) connection caused 23 (0.015% incidence) occlusions between pump connector and catheter and 34 disconnections (0.22% incidence)

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Key Question 3

- Is there any evidence of differential efficacy or safety issues amongst special populations?

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KQ3: Differential Efficacy/Safety

- Nothing found in literature
- Our statistical tests in KQ1 did not find any factors related to differential efficacy, and reporting in primary studies precluded testing for differential safety
- Due to an absence of evidence, no conclusions can be drawn

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Findings

Costs and Cost Effectiveness

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Key Question 4

- What are the cost implications and cost effectiveness for implantable infusion pumps?

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Key Question 4: Costs

- Complex array of costs (e.g., screening, initial purchase, pump implantation, medication refills, consultations, complications, adjunctive medications, pump replacement or removal)
- 4 cost analyses
- Bottom line: inconclusive evidence

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de Lissovoy (1997)

- 5-year cost model of pump vs. non-pump
- Failed back surgery syndrome
- Incorporated numerous types of costs
- Estimated probabilities of various events

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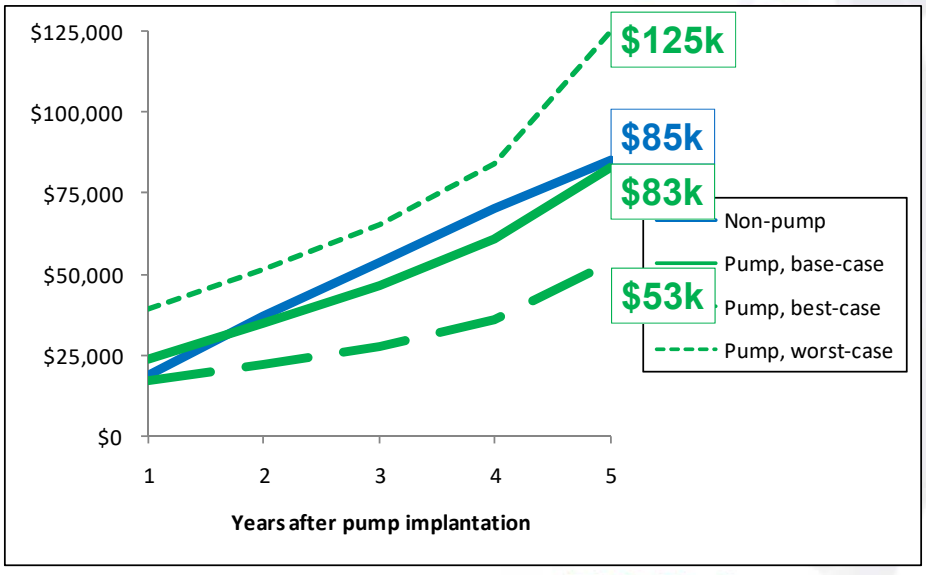

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de Lissovoy (1997)

- Modelled data, not an empirical study
- 11 years old
- Large uncertainty around the base case
  - (Range $53,000 to $125,000 total cost for 5 years of treatment)

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Kumar (2000)

- Five-year empirical cost study of 67 FBSS patients
- Canada
- Selection for response in the pump group (N=23/44), but not the control group (N=44/44)
- Numerous types of costs
- Five-year pump cost $44k USD (range $42k to $46k)
- Five-year non-pump cost $56k USD (greater need for supplemental treatments)

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Reden and Anders (2006)

- Insurance claims data from 1,647 patients
- Some may not have had chronic non-cancer pain
- Used Washington-state-specific fee schedules
- Hypothetical non-pump cost estimated based on the single month prior to pump implantation ($4k/month)
- Method 1: no ongoing cost savings from the pump
- Method 2: ongoing cost savings

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Reden and Anders (2006)

- Non-pump, total 30-year cost: $2.00M
- Pump, total 30-year cost, using Method 1: $2.18M
- Pump, total 30-year cost, using Method 2: $1.54M

- Single month before implantation may not be representative ($4k/month)
- Inclusion of other types of patients

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Anderson (2003)

- A different research question: whether to screen for the pump intrathecally or epidurally
- N=18 intrathecal, N=19 epidural
- Intrathecal screening $1.9k vs. epidural screening $4.8k
- Also shorter hospital stay

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Conclusions: Cost Issues and Cost-Effectiveness

- Four cost analyses, all inconclusive
- Uncertainty, older data, Canada, selection bias, unrepresentative costs, inclusion of other patients

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Conclusions

- Implanted infusion pumps for the delivery of intrathecal opioids are associated with clinically significant reduction in pain on average, but most other outcomes, including cost issues, were inconclusive
- Implanted infusion pumps for the delivery of intrathecal opioids are not successful in every patient
- Most of the adverse events were minor, but serious events, including re-operation, also occured
- Areas for further research may include identification of patients most likely to benefit from, or be harmed by, implanted infusion pumps or infused drugs, and measurement of quality of life and functional status outcomes using validated tools

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▷ Questions?

HTCC Coverage and Reimbursement Determination Analytic Tool

HTA's goal is to achieve *better health care outcomes* for enrollees and beneficiaries of state programs by paying for proven health *technologies that work*.

To find best outcomes and value for the state and the patient, the HTA program focuses on these questions:

1. Is it safe?
2. Is it effective?
3. Does it provide value (improve health outcome)?

The principles HTCC uses to review evidence and make determinations are:

Principle One: Determinations are Evidence based

HTCC requires scientific evidence that a health technology is safe, effective and cost-effective[1] as expressed by the following standards. [2]

- Persons will experience better health outcomes than if the health technology was not covered and that the benefits outweigh the harms.
- The HTCC emphasizes evidence that directly links the technology with health outcomes. Indirect evidence may be sufficient if it supports the principal links in the analytic framework.
- Although the HTCC acknowledges that subjective judgments do enter into the evaluation of evidence and the weighing of benefits and harms, its recommendations are not based largely on opinion.
- The HTCC is explicit about the scientific evidence relied upon for its determinations.

Principle Two: Determinations result in health benefit

The outcomes critical to HTCC in making coverage and reimbursement determinations are health benefits and harms.[3]

- In considering potential benefits, the HTCC focuses on absolute reductions in the risk of outcomes that people can feel or care about.
- In considering potential harms, the HTCC examines harms of all types, including physical, psychological, and non-medical harms that may occur sooner or later as a result of the use of the technology.
- Where possible, the HTCC considers the feasibility of future widespread implementation of the technology in making recommendations.
- The HTCC generally takes a population perspective in weighing the magnitude of benefits against the magnitude of harms. In some situations, it may make a determination for a technology with a large potential benefit for a small proportion of the population.
- In assessing net benefits, the HTCC subjectively estimates the indicated population's value for each benefit and harm. When the HTCC judges that the balance of benefits and harms is likely to vary substantially within the population, coverage or reimbursement determinations may be more selective based on the variation.
- The HTCC considers the economic costs of the health technology in making determinations, but costs are the lowest priority.

[1] Based on Legislative mandate: See RCW 70.14.100(2).

[2] The principles and standards are based on USPSTF Principles at: http://www.ahrq.gov/clinic/ajpmsuppl/harris3.htm

[3] The principles and standards are based on USPSTF Principles at: http://www.ahrq.gov/clinic/ajpmsuppl/harris3.htm

Using Evidence as the basis for a Coverage Decision

Arrive at the coverage decision by identifying for Safety, Effectiveness, and Cost whether (1) evidence is available, (2) the confidence in the evidence, and (3) applicability to decision.

1. Availability of Evidence:

Committee members identify the factors, often referred to as outcomes of interest, that are at issue around safety, effectiveness, and cost. Those deemed key factors are ones that impact the question of whether the particular technology improves health outcomes. Committee members then identify whether and what evidence is available related to each of the key factors.

2. Sufficiency of the Evidence:

Committee members discuss and assess the evidence available and its relevance to the key factors by discussion of the type, quality, and relevance of the evidence[4] using characteristics such as:

- Type of evidence as reported in the technology assessment or other evidence presented to committee (randomized trials, observational studies, case series, expert opinion);
- the amount of evidence (sparse to many number of evidence or events or individuals studied);
- consistency of evidence (results vary or largely similar);
- recency (timeliness of information);
- directness of evidence (link between technology and outcome);
- relevance of evidence (applicability to agency program and clients);
- bias (likelihood of conflict of interest or lack of safeguards).

Sufficiency or insufficiency of the evidence is a judgment of each clinical committee member and correlates closely to the GRADE confidence decision.

Not Confident	Confident
Appreciable uncertainty exists. Further information is needed or further information is likely to change confidence.	Very certain of evidentiary support. Further information is unlikely to change confidence

3. Factors for Consideration - Importance

At the end of discussion at vote is taken on whether sufficient evidence exists regarding the technology's safety, effectiveness, and cost. The committee must weigh the degree of importance that each particular key factor and the evidence that supports it has to the policy and coverage decision. Valuing the level of importance is factor or outcome specific but most often include, for areas of safety, effectiveness, and cost:

- risk of event occurring;
- the degree of harm associated with risk;
- the number of risks; the burden of the condition;
- burden untreated or treated with alternatives;
- the importance of the outcome (e.g. treatment prevents death vs relief of symptom);
- the degree of effect (e.g. relief of all, none, or some symptom, duration, etc.);
- value variation based on patient preference.

[4] Based on GRADE recommendation: http://www.gradeworkinggroup.org/FAQ/index.htm

HEALTH TECHNOLOGY EVIDENCE IDENTIFICATION

Discussion Document: What are the key factors and health outcomes and what evidence is there?

Safety Outcomes	Safety Evidence
Efficacy/Effectiveness Outcomes	**Efficacy/Effectiveness Evidence**
Cost Outcomes	**Cost Evidence**
Other Factors	**Evidence**

Medicare Coverage and Guidelines

Organization	Date	Outcome	Evidence Cited?	Grade / Rating
Medicare	1994* (other portions updated 2004)	Permanent intrathecal pump implantation is covered with criteria: • Life expectancy of at least three months • Unresponsive to less invasive medical therapy, such as systemic opioids and attempts to correct underlying physical and psychological abnormalities • Successful intraspinal opioid trial, defined by acceptable pain relief and side effects and their impact on daily living, and patient acceptance	Y*	Not rated by ECRI
American Society of Interventional Pain Physicians (Boswell et. al)	2007	Evidence for implantable intrathecal infusion systems is strong for the short term improvement in pain of malignant or neuropathic pain. The evidence is moderate for long term management of chronic pain.	Y	Not rated by ECRI
Sisken Hospital for Physical Rehabilitation (Sanders et. al)	2005	Studies and systematic reviews regarding the efficacy of infusion pumps and spinal cord stimulators have increased. Thus far, they have not met the current criteria for adequate supportive evidence to recommend application to CPS (chronic pain syndrome) patients	Y	Not rated by ECRI
International Research Foundation for RSD/CRPS (Kirkpatrick et. al.)	2003	No conclusion offered, however authors note that “morphine pumps” have not been clinically shown to be superior to oral morphine.	N	Not rated by ECRI

*A national coverage decision for infusion pumps (manual section 280.14) was issued in February 1994 as durable medical equipment. The latest version of the policy was adopted December 17, 2004. The initial determination included implantable infusion pumps for epidural or intrathecal administration of opioid drugs for chronic non-cancer pain was not updated since 2004.
*This decision was based on a technology assessment completed in 1994 by the Office of Health Technology Assessment (OHTA) and used the only available literature which was from 1984-1992.

Clinical Committee Evidence Votes

First voting question
The HTCC has reviewed and considered the technology assessment and information provided by the administrator, reports and/or testimony from an advisory group, and submissions or comments from the public. The committee has given greatest weight to the evidence it determined, based on objective factors, to be the most valid and reliable.

Is there sufficient evidence under some or all situations that the technology is:

	Inconclusive (no)	**Equivalent** (yes)	**Less** (yes)	**More** (yes)
Effective				
Safe				
Cost-effective				

Discussion
Based on the evidence vote, the committee may be ready to take a vote on coverage or further discussion may be warranted to understand the differences of opinions or to discuss the implications of the vote on a final coverage decision.

- Evidence is insufficient to make a conclusion about whether the health technology is safe, efficacious, and cost-effective;
- Evidence is sufficient to conclude that the health technology is unsafe, ineffectual, or not cost-effective
- Evidence is sufficient to conclude that the health technology is safe, efficacious, and cost-effective for all indicated conditions;
- Evidence is sufficient to conclude that the health technology is safe, efficacious, and cost-effective for some conditions or in some situations

A straw vote may be taken to determine whether, and in what area, further discussion is necessary.

Second vote
Based on the evidence about the technologies' safety, efficacy, and cost-effectiveness, it is

_____Not covered. _____ Covered Unconditionally. _____Covered under certain conditions.

Discussion Item

Is the determination consistent with identified Medicare decisions and expert guidelines, and if not, what evidence is relied upon.

Clinical Committee Findings and Decisions

Next Step: Cover or No Cover
If not covered, or covered unconditionally, the Chair will instruct staff to write a proposed findings and decision document for review and final adoption at the following meeting.

Next Step: Cover With Conditions
If covered with conditions, the Committee will continue discussions.

1) Does the committee have enough information to identify conditions or criteria?
   - Refer to evidence identification document and discussion.
   - Chair will facilitate discussion, and if enough members agree, conditions and/or criteria will be identified and listed.
   - Chair will instruct staff to write a proposed findings and decision document for review and final adoption at next meting.

2) If not enough or appropriate information, then Chair will facilitate a discussion on the following:
   - What are the known conditions/criteria and evidence state
   - What issues need to be addressed and evidence state

The chair will delegate investigation and return to group based on information and issues identified. Information known but not available or assembled can be gathered by staff ; additional clinical questions may need further research by evidence center or may need ad hoc advisory group; information on agency utilization, similar coverage decisions may need agency or other health plan input; information on current practice in community or beneficiary preference may need further public input. Delegation should include specific instructions on the task, assignment or issue; include a time frame; provide direction on membership or input if a group is to be convened.

Efficacy Considerations:

- What is the evidence that use of the technology results in more beneficial, important health outcomes? Consider:
    - Direct outcome or surrogate measure
    - Short term or long term effect
    - Magnitude of effect
    - Impact on pain, functional restoration, quality of life
    - Disease management
- What is the evidence confirming that use of the technology results in a more beneficial outcome, compared to no treatment or placebo treatment?
- What is the evidence confirming that use of the technology results in a more beneficial outcome, compared to alternative treatment?
- What is the evidence of the magnitude of the benefit or the incremental value
- Does the scientific evidence confirm that use of the technology can effectively replace other technologies or is this additive?
- For diagnostic tests, what is the evidence of a diagnostic tests' accuracy
    - Does the use of the technology more accurately identify both those with the condition being evaluated and those without the condition being evaluated?
- Does the use of the technology result in better sensitivity and better specificity?
- Is there a tradeoff in sensitivity and specificity that on balance the diagnostic technology is thought to be more accurate than current diagnostic testing?
- Does use of the test change treatment choices

Safety

- What is the evidence of the effect of using the technology on significant morbidity?
    - Frequent adverse effect on health, but unlikely to result in lasting harm or be life-threatening, or;
    - Adverse effect on health that can result in lasting harm or can be life-threatening.
- Other morbidity concerns
- Short term or direct complication versus long term complications
- What is the evidence of using the technology on mortality – does it result in fewer adverse non-fatal outcomes?

Cost Impact

- Do the cost analyses show that use of the new technology will result in costs that are greater, equivalent or lower than management without use of the technology?

Overall

- What is the evidence about alternatives and comparisons to the alternatives
- Does scientific evidence confirm that use of the technology results in better health outcomes than management without use of the technology?