



Clinical Commissioning Policy: Intrathecal Pumps for Treatment of Severe Cancer Pain

Reference: NHS England: D08/P/b

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Document Status

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1 Executive Summary

Policy Statement

NHS England will routinely commission intrathecal pumps for the treatment of severe cancer pain in accordance with the criteria outlined in this document.

In creating this policy NHS England has reviewed this clinical condition and the options for its treatment. It has considered the place of this treatment in current clinical practice, whether scientific research has shown the treatment to be of benefit to patients, (including how any benefit is balanced against possible risks) and whether its use represents the best use of NHS resources.

This policy document outlines the arrangements for funding of this treatment for the population in England.

Equality Statement

NHS England has a duty to have regard to the need to reduce health inequalities in access to health services and health outcomes achieved as enshrined in the Health and Social Care Act 2012. NHS England is committed to fulfilling this duty as to equality of access and to avoiding unlawful discrimination on the grounds of age, gender, disability (including learning disability), gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, gender or sexual orientation. In carrying out its functions, NHS England will have due regard to the different needs of protected equality groups, in line with the Equality Act 2010. This document is compliant with the NHS Constitution and the Human Rights Act 1998. This applies to all activities for which NHS England is responsible, including policy development, review and implementation.

Plain Language Summary

The pain associated with cancer can for the most part be managed without specialised interventions. However, Intrathecal Drug Delivery plays an important role in the treatment of intractable (hard to control) pain in a small group of appropriately selected patients, with an associated significant reduction in quality of life and that have no other treatment options. The needs of this population can be variable and as a consequence the selection process requires a highly specialised team to ensure

appropriate selection and safety criteria as well as equity of access. It is for these reasons NHS England funds this treatment.

Intrathecal Drug Delivery (ITDD) enables clinicians to formulate individualized treatment regimens that can provide significantly improved analgesia (pain relief) with smaller doses, and fewer adverse effects than traditional opioid-based (morphine & morphine - like) therapies in a small group of highly selected patients and where other techniques have failed or are not indicated.

NHS England will routinely commission the use of ITDD to treat severe refractory pain in appropriately selected patients with the diagnosis of cancer related pain. There is a clinical need for this service that is supported by class 1 evidence on treatment efficacy and safety compared with usual care. Use of this therapy will be commissioned by NHS England as a prescribed service in specialised pain centres acting as lead centres to agreed geographical pain networks, to ensure right patient selection, strict clinical vigilance and safety arrangements as well as equity of access to the treatment.

It is a combination of the selection processes, ITDD Team expertise, associated support network and overall centre organisation that makes therapy with ITDD successful and as a consequence appropriate for NHS England to fund.

2 Introduction

Intrathecal drug delivery (ITDD) systems offer an alternative to other routes of analgesic administration for appropriately selected patients with severe intractable cancer pain.

Cancer pain may arise from a tumour compressing or infiltrating tissue. In addition to this, pain occurs in 67% of patients with metastatic cancer. Treatments such as chemotherapy, radiation and surgery may produce painful conditions that persist long after treatment has ended. .

Cancer pain can be controlled in the majority of patients by following the WHO guidelines. Approximately 5-15% of cancer patients have refractory pain and require advanced techniques. In this situation, systemic drugs may relieve pain but may also

have serious side effects including sedation, constipation, respiratory depression and fatigue that significantly impact on quality of life. In some patients systemic drugs will not reduce the pain without significant sedation.

In a prospective study of 2118 patients with cancer pain managed by the WHO guidelines, 8% required nerve blocks, 3% neurolytic blocks and 3% spinal analgesia (epidural/intrathecal)ⁱ. Neurolytic or neuroablative interventions may be appropriate alternative interventions for some patients with intractable cancer pain, especially when the prognosis is less than a year.

ITDD systems are an advanced stage intervention and are only indicated where other conservative interventions have failed or are contraindicated and where the uncontrolled pain is causing a significant impact on physical and mental health. Uncontrolled cancer related pain (e.g. incident pain) treated with escalating dosages of opioids may lead to life-threatening complications related to excessive sedation and other systemic complications (e.g. pneumonia) leading on to early death.

By positioning a catheter in the cerebrospinal fluid, ITDD allows smaller doses of drugs to be applied directly to the receptors of the central nervous system, achieving pain relief with much smaller doses and as a consequence fewer side effects, than with oral or parenteral routes. There are many reports of improved pain control and fewer complications with the intrathecal route.

History

Opioid receptors were identified in the spinal cord in 1973ⁱⁱ. Subsequent animal studies demonstrated that intrathecal opioids produce excellent and highly selective analgesiaⁱⁱⁱ. Cousins in 1979 used the phrase 'selective spinal analgesia' to describe the phenomenon that spinally administered opioids could produce a specific analgesic effect with few motor, sensory or autonomic side effects^{iv}. The first clinical use of epidural and intrathecal opioids followed^{v,vi}. It was subsequently demonstrated that the analgesic effect was, in the main, due to the uptake of the opioid directly into the spinal cord^{vii}.

Intrathecal Drugs

Intrathecal morphine and baclofen are approved for this use by FDA. Other drugs are commonly used and are agreed by international panel of experts and are published in polyanalgesic consensus conference 2012.

Intrathecal opioids exert their analgesic effect pre and post synaptically by reducing neurotransmitter release and by hyperpolarising the membranes of neurones in the dorsal horn, thus inhibiting pain transmission.^{viii}

Intrathecal local anaesthetics exert their effect by sodium channel blockade, which inhibits the action potential in neural tissue in the dorsal horn, producing a reversible analgesic effect. They also have an action on the intrathecal part of the nerve root.

Intrathecal clonidine, a α_2 agonist, modulates pain transmission by suppression of the release of the C fibre neurotransmitters, Substance P and Calcitonin Gene Related Peptide (CGRP). It has been hypothesised that clonidine also suppresses preganglionic sympathetic outflow.

This document is intended to define and support best practice and provide guidance for:

- Specialist MDTs and institutions delivering or planning to deliver the treatment
- Referrers, secondary care, primary care, health professionals and carers regarding the management of patients with implanted intrathecal drug delivery (ITDD) systems
- Commissioners of health care as to the nature of the technique and when it might be used

The document describes the policy for the commissioning of ITDD systems for clinical use in the management of cancer related pain and provides recommendations for the clinical and governance context in which this therapy should be delivered.

It covers the clinical indications in which pain relief is the major indication for the technique.

These recommendations are based upon synthesis and interpretation of published evidence and upon the consensus of expert opinion of the Clinical Reference Group for Specialised Pain.

3 Definitions

- Intrathecal drug delivery system/PUMP for Drug delivery (ITDD) – In this policy ITDD is the name of the treatment and device.
 - Intrathecal catheter – Part of an ITDD device that is placed within the spinal cerebrospinal fluid (subarachnoid space) to infuse pain medication stored in the pump reservoir. It is inserted via a needle, as a percutaneous technique or via a cut down open procedure depending on the difficulty of insertion.
 - Implantable pump reservoir – Contains the drug, which is infused very slowly in to the cerebrospinal fluid and a power source that drives the pump.
 - Programmable pumps allow variable flow to more easily titrate the daily dose to that which suits the individual patient. Programmable pumps are the gold standard of ITDD.
- Trial of ITDD – A test period by which the patient can experience pain relief and improvement in function from a temporary application of drug to the cerebrospinal fluid. The result from the trial is essential towards the decision for permanent implantation.
- Severe, chronic pain - Chronic pain which is continuous, long-term pain of either more than 12 weeks (6 months, 12 months according to other definitions) or after the time that healing would have been thought to have occurred in pain after trauma or surgery.

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- Intractable pain – Pain, which despite expert management is unresponsive or poorly responsive to conventional medical management or where the conventional pain relief causes unacceptable side effects.
- Neuropathic pain is pain initiated or caused by a primary lesion or dysfunction in the peripheral or central nervous system. For example nerve infiltration by cancer or nerve damage associated with radiotherapy
- Nociceptive pain - Pain caused by local damage to tissues.
- Incident pain - Severe cancer related pain caused in response to an event (e.g. movement and no pain at rest). This type of pain responds poorly to conventional painkillers including opioids.

Examples of cancer pain

- Colorectal Cancer can spread with metastasis throughout pelvic and rectal areas leading on to infiltration of surrounding soft tissue and nerves and this can cause pelvic but also lower limb pain and have an impact on bladder and bowel function.
- Kidney cancer may spread to bones leading on to pathological fracture, which can cause severe movement related pain (incident pain). This can be very difficult to treat with strong opioids but needs further input from other disciplines for effective pain relief (e.g. surgical fixation of fracture), improvements in quality of life and activities of daily living.
- Pelvic cancer such as bone sarcoma, cervical or rectal cancer causing mixed nociceptive and neuropathic pain with visceral pain.

Outcome measures

Measures of pain and pain relief, change of function, improvement in quality of life, reduction in oral pain medications and decrease in toxic side effects from systemic drugs.

Outcome Indices will include BPI (Brief Pain Inventory), Visual Analogue Scale for Pain, NRS (Numerical Rating Scale), SF-36, BDI (Beck Depression Inventory), PDI (Pain Disability Index), BPI (Brief Pain Inventory), EQ5D-5L, MPQ (McGill Pain Questionnaire) and Patient's Global impression of change.

The National Neuromodulation Registry (NNR) will be available for the systematic collection of patient and device data on demography, disease severity and outcomes for all patients implanted with ITDD. The outcomes used are BPI, EQ5D-5L, Global impression of change, Intrathecal drug combinations and daily doses. NNR is sponsored by the Neuromodulation Society of UK and Ireland (NSUKI) and has been created in partnership with the National Institute of Cardiovascular outcomes and Research (NICOR)

Timing of assessment

Patients with cancer related pain should have quick access (within weeks) to comprehensive assessment within MDT including, Pain Medicine, Palliative Medicine and Oncology as applicable and available locally.

4 Aims and Objectives

This policy aims to:

- Present the policy recommendations and rationale.

The objectives are to:

- Assess the evidence base on the efficacy and safety of Intrathecal Pumps (ITDD) in the treatment of severe, chronic cancer pain.
- Achieve a clinical consensus
- Derive policy recommendations for implementation

5 Epidemiology and Needs Assessment

The Health Survey for England (2011)¹¹ published in December 2012 highlights that current service provision for pain management is inadequate and existing services are not evenly distributed across the country. The Chief Medical Officer's Annual Report (2008) had a similar view on pain services provision in England. In order to look at the quality and provision of existing pain services, the National Pain Audit was commissioned. The report from phase one of the audits has highlighted that there are areas to be improved, particularly around the provision of multidisciplinary services for pain management.

European data as in table 1 reflects poor uptake of ITDD treatment generally in UK. This has to be considered in the context of the intractable nature of symptoms, disability and cost-effective data now available for spasticity and chronic pain including cancer pain.

6 Evidence Base

A literature search restricted to randomised control trials and systematic reviews was undertaken and a summary of the evidence is presented below. Research in cancer pain and ITDD is difficult as there are ethical issues around double blind randomised trials in a group of patients that are suffering significantly with poor quality of life due to severe pain and may have limited survival. It may also be unethical to subject them to another randomized controlled trial while high quality evidence may already be available as in case of this therapy.

Clinical effectiveness and safety

One systematic review was identified which evaluated the efficacy and safety of intrathecal infusions used in long-term management (> 6 months) of chronic refractory cancer pain (Hayek et al. 2011)¹⁴. It identified 5 studies in total, which met its inclusion criteria - 1 randomised controlled trial (RCT) and 4 observational studies. The authors concluded that the recommendation for intrathecal infusion systems for cancer-related pain is a moderate recommendation based on the high quality of evidence.

The RCT included in the systematic review compared the efficacy of intrathecal drug therapy in association with conventional medical management (CMM) with CMM alone for intractable mixed neuropathic and nociceptive refractory cancer related pain (Smith et al. 2002)¹⁵. Refractory cancer pain was defined as patients reporting a Visual Analogue Scale (VAS) score greater than or equal to 5 despite 200 mg/day oral morphine equivalents. Those assigned to the CMM group received all pain therapy except spinally administered drugs, cordotomy, or other similar neurosurgical interventions. Those who received the ITDD started with morphine but could receive other analgesics if morphine proved to be inadequate for pain relief, using algorithms outlined by Staats (1999)¹⁶. Success was defined as improvement in VAS or reduction in toxicity as primary outcomes at 4 weeks follow up; 60/71 (84.5%) ITDDS patients achieved success, as compared to 51/72 (70.8%) CMM patients. The mean CMM VAS score fell from 7.81 to 4.76 (39% reduction); for the ITDD group, the scores fell from 7.57 to 3.67 (52% reduction, $P = 0.055$) - 13% mean reduction between the groups. The mean CMM toxicity scores fell from 6.36 to 5.27 (17% reduction); for the ITDDS group, the toxicity scores fell from 7.22 to 3.59 (50% reduction, $P=0.004$). The ITDDS group had significant reductions in fatigue and depressed level of consciousness ($P < 0.05$). ITDD patients had improved survival, with 53.9% alive at 6 months compared with 37.2% of the CMM group ($P = 0.06$).

A further follow-up study of the RCT found at 12 weeks the ITDDS VAS pain scores decreased from 7.81 to 3.89 (47% reduction) compared with 7.21 to 4.53 for non-ITDDS patients (42% reduction; $P = 0.23$). The 12 week drug toxicity scores for ITDDS patients decreased from 6.68 to 2.30 (66% reduction), and for non-ITDDS patients from 6.73 to 4.13 (37% reduction; $P = 0.01$). All individual drug toxicities improved with ITDDS at both 4 and 12 weeks. At 6 months, 32% of the group randomized to CMM and who did not cross over to ITDDS were alive, compared with 52%–59% for patients in those groups who received ITDDS.

In the RCT by Smith et al. (2002), a total of 194 serious complications were reported, split evenly between the 2 groups¹⁵. Of the 99 complications in the ITDD arm, 14 were related to the “implanted pump or related procedure,” 10 requiring revision and one requiring ex-plant (Smith et al. 2002).

Cost – Effectiveness For Cancer Pain

A cost minimisation analysis demonstrated that unlike other routes of opioid administration (oral, subcutaneous, intravenous, transdermal), costs associated with ITDD remained stable over time, irrespective of dosage escalation (e.g. 5% dosage increase) and treatment duration. After 3-6 months of opioid therapy, intrathecal delivery begins to cost less than epidural, subcutaneous and intravenous. Although costs of surgical pump placement for ITDD initially appear high, they attenuate over time, depending on the duration of patient survival. The latter represent 80% of the total charges compared with oral/transdermal opioid medication accounting for more than half of the total charges associated with the treatment of chronic cancer pain. In addition to the later medication costs, significant costs are also incurred by prolonged inpatient length of stay for pain management (Gerhard MS et al. 1994).

A retrospective chart review on 36 cancer patients showed that in the high cost conventional opioid group, the median daily cost of opioid medications was \$172.47 compared with \$16 in the ITDD group. In the latter selected group, ITDD became cost – efficient within 6 months (Brogan SE et al. 2013).

7 Rationale behind the Policy Statement

It is acknowledged that severe, chronic refractory pain represents a therapeutic challenge for a distressing area of unmet need for which additional treatment options would be welcomed. In cancer pain, recent systematic reviews have concluded that the recommendation is ‘moderate’, based on a higher quality (RCT and observational studies) of evidence.

8 Criteria for Commissioning

This policy has been agreed on the basis of NHS England’s understanding of the likely price of care associated with enacting the policy for all patients for whom NHS England has funding responsibility, as at the time of the policy’s adoption. Should these prices materially change, and in particular should they increase, NHS England may need to review whether the policy remains affordable and may need to make revisions to the published policy.

Overview

ITDD for cancer related pain will be reserved for a small number of appropriately selected patients (see below) that meet the same stringent criteria and have been assessed by a specialised pain management service or a designated experienced centre linked to a specialised pain management service. In addition to careful clinical selection, a trial of intrathecal drugs will normally be performed to ensure efficacy prior to implant. The nature of the trial will be appropriate to the needs of the patient. For cancer related pain with a life expectancy of less than 2 years it is likely that an intrathecal bolus test or short-term intraspinal catheter test will be sufficient to confirm pain relief. In patients with a longer life expectancy where ITDD is a means to augment some rehabilitation, a longer duration of trial (1 to 2 weeks) of intraspinal catheter in a hospital and then domiciliary environment is appropriate. This will be accompanied by a rigorous and objective assessment of pain relief, analgesic requirements and improvement in function.

Proper patient selection, implantation technique, maintenance and continued clinical and equipment vigilance are paramount to ensure success and reduce complications.

Moreover all future ITDD treated patients will be entered onto the National Neuromodulation Registry to allow a long term observational audit of outcomes. The use of ITDD to treat severe cancer pain will be routinely funded for the following selected group of patients:

Indications and contraindications

Patients who meet all of the following criteria:

- Patients who have severe pain of known origin that has failed to be satisfactorily managed despite conventional and specialised pain

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management or where that pain control is partially achieved but with unacceptable side effects. They will have been assessed against WHO analgesic ladder and for other specialty (radiotherapy or surgical treatments including surgical fixation of pathological fracture and palliative tumor resection) and specialized techniques such as spinal cord stimulation, neurosurgical interventions including cordotomy and complex drugs by a specialized team with the skill to identify treatment needs. As well as pain medicine, palliative medicine and oncology services will be involved in shared decision making with the patient and their family.

- All patients will have been previously assessed by a multidisciplinary pain management service and following a trial of properly managed oral/transdermal opioids which achieve some pain reduction but their continued use is limited by high opioid toxicity.
- Severe, poorly controlled cancer related pain usually perceived below the diaphragm (e.g. spinal, pelvic or lower limb tumour) and managed within an appropriate setting i.e. in liaison with palliative medicine/oncology.
- Patient has been referred to, assessed and is under the care of a Specialised Pain Management centre and MDT (with expertise, experience, follow up capability and staffing levels to support the safe use and delivery of ITDD, on a 24/7 basis).
- Patient has received a structured pain assessment with an accurate formulation of both psychological and physical factors contributing to pain by the multi-disciplinary team experienced in ITDD therapy^{ix}. This will include baseline pain characteristics, pain intensity and severity scores, prior medications (anticoagulants, chemotherapy etc.), alcohol/recreational drug use/abuse, co-existing medical conditions, infection risk, immunosuppression, concurrent pain medications and psychological evaluation for stability. Other patient selection criteria will include consideration of social and medical support systems, prognosis and life expectancy.

- Patient has undergone a successful trial of intraspinal opioids (where appropriate) with an emphasis on side-effects and efficacy. This is key to success and will be clearly identified in the records.

Exclusions

Patients who meet with any of the following criteria should not receive ITDD:

- History of psychosis, active suicidal or homicidal behaviour, major uncontrolled depression, or anxiety, or serious cognitive deficits. ITDD therapy is relatively contraindicated for the above and these primary conditions need to be treated or optimised first.

Absolute contra-indications are:

- Pregnancy or nursing mother or planning to get pregnant
- Any concomitant treatment or medical condition that would render ITDD administration hazardous
- Infection
- Uncorrectable bleeding disorder
- Logistical difficulties with after care including pump refills, funding of ongoing ITDD.

9 Patient Pathway

The following pathway criteria will have to be fulfilled:

Referrals

Referrals to MDT lead of specialised pain centre only from networked secondary care pain services or other tertiary specialties e.g. palliative medicine, cancer centre, orthopaedic (bony metastases). This should be a tertiary referral service providing equity of access over England. Currently we estimate there are about 50 new implants a year and that those implanted are expected to have a life expectancy of greater than three months with only a few living beyond a few years.

MDT

There should be a designated team that comprises the implanter, typically an interventional pain specialist (or neurosurgeon for the implant), nurse specialists, pharmacists, psychologists and physiotherapists as appropriate with specialised training and experience in the field. All those involved in implantation, fill and refill procedures and follow-up must maintain appropriate continuous professional development.

It is recognised that the management of each condition is specialised. The specialised team will work jointly with the patient's primary care team, referring secondary care pain teams and the clinical teams with responsibility for the primary condition. All MDT professionals have a role in patient assessment, choice of therapy, assessment of response and continuous management. The MDT should assess the potential benefits and risks of ITDD for the individual patient and discuss them with the patient. The patient and carers must be a part of decision making.

Treatment, Monitoring and Follow-up

All reversible and treatable causes of pain should be addressed before ITDD is undertaken. This should include the appropriate application of less invasive pain management therapies before initiation of ITDD. The patient's narrative should be supplemented by objective records from referring clinicians.

A thorough physical examination including spinal and neurological examination and for co-morbidities that could increase the risk of ITDD should be carried out. Co-morbidities such as, Obstructive Sleep Apnoea, diabetes, obesity, metabolic syndrome or chronic lung, cardiac or kidney disease or smoking will increase the risk of complications. All comorbidities should be well managed before commencing ITDD therapy.

Patients with a severe cancer related pain diagnosis may also have depression, anxiety, PTSD, substance abuse concerns, cognitive impairment or personality disorder. CBT and psychological support should be available.

Final approval of a patient's suitability for ITDD rests with the MDT.

Comprehensive patient/caregiver education (on efficacy, side-effects of ITDD, risks and benefits) and informed consent are essential elements of the process. Patients should also know that achieving an appropriate balance between pain management (optimisation) and side-effects (minimisation) takes time and may require slow titration with continuing adjustments. Patients should understand that the outcome of ITDD is one of pain management and not of pain cure. ITDD requires a candid therapeutic partnership in which the patient takes responsibility for adherence to the physician's recommendations, self-monitoring and vigilance for adverse effects. A patient who cannot partner in this way or who does not have a caregiver who can fulfil this role should not be implanted.

Endocrine input should be available in patients with suspected long term survival e.g. longer than one year.

Trial of ITDD

All patients considered for ITDD should have a trial. A trial provides an opportunity to assess short-term pain relief, gauge dosing, determine individual tolerability, and assesses an individual's response to ITDD and also to monitor patient safety. Trial will depend on patient needs. An appropriate assessment needs to be undertaken as to nature of pain and current medication as well as other medical conditions and treatments. Prior to the trial the treatments should be optimised. For the duration of the trial, optimisation may involve drug changes, such as converting to shorter acting drugs and drug reductions.

The experienced clinician would undertake the trial after discussion with the team and having made decisions on optimisation of the patient and doses of trial drugs.

The trial should involve fluoroscopy x-ray imaging and level of insertion takes in to account previous MRI/CT scan imaging discussed at a MDT.

The trial may be single shot or continuous infusion, epidural or intrathecal depending on patient requirements.

Post procedure the patient should be nursed in a facility experienced in managing such patients and eventually on a ward also familiar with high dose patients and neuroaxial drug delivery.

Refills

Post ITDD implant, the initial titration of drugs will occur with direct involvement of the experienced Pain Management Consultants at the main centre. Once stabilised refills could be undertaken at agreed centres specifically trained up, supported by the MDT. As the patient's condition progresses decisions about continued care would be agreed.

Ongoing Care

Patients with intrathecal implants require ongoing attention and care including programming, prescription adjustments, refills, monitoring of efficacy and disease progression. Dose increases should be titrated slowly to minimise adverse effects and allow patients to develop tolerance. Dose increases should not generally occur more frequently than at once weekly intervals and should not exceed 30% of the total infused daily dose. More rapid dose titration may be suitable for patients with cancer pain. At every refill, patients and care-givers should be reminded about the symptoms and signs of overdose, underdose and withdrawal and instructed to seek medical assistance should they experience these.

These resources must be planned and arranged appropriately. Dedicated refill sessions are recommended, conducted by suitably trained and competent nurse specialists or doctors, in dedicated procedure room. The hospital pharmacy must be involved with aseptic, traceable production of prescribed drugs and admixtures. This will require an understanding that drugs and drug admixtures are being used outside pharmacological license although guided by best practice as determined by the annual reviews of the polyanalgesic consensus. A thorough system for prescription in advance must be created and adhered to. Drug admixture pump program, prescriptions should be double checked by a competent nurse or doctor before the patient leaves. As complications are potentially life threatening, arrangements must be in place for 24/7 medical cover. Those undertaking refill procedures should be familiar with the technique and aware of the importance and significance of

neurological symptoms and signs, failure of pain relief and also the clinical signs of overdose.

Extreme vigilance must be given to all aspects of safety, particularly the prevention of the inadvertent administration of drugs by the wrong route. Design of systems and equipment to protect against this error should be encouraged. Patient and carer engagement in checking the route should be encouraged. Drugs and drug mixtures for intrathecal use should be pre-prepared in appropriate sterile conditions and be preservative free and be compatible with the pump. Stability and compatibility of admixtures must be addressed. Off license use of drug admixtures (only as recommended in Polyanalgesic consensus - PACC) should be carefully explained to the patient. The reasons for such use and the possible sequelae explained and documented. In many situations, better efficacy and reduced side effects are achieved with appropriate drug admixtures.

Different pumps will have different drug compatibilities. The ITDD team must have a thorough knowledge of this and the type of pump

Adequate arrangements for ongoing care should be in place to include programme changes and refill attendances. Refill intervals must not be open ended; the stability of the drug is an important consideration and determines the interval.

Education of the primary care team, patient and the patient's family must be provided. Primary and secondary care staff should be aware of the nature and initial management of complications. Links with implant manufacturers and distributors are important for ongoing support and education.

Complications and Their Management

At each visit patients should be encouraged to report any changes in pain control, side-effects or new neurological symptoms. An examination should follow if neurological symptoms are reported. An MRI scan maybe required to exclude catheter tip granuloma.

Patient education should cover the clinical signs of overdose, including dizziness, sedation, euphoria, anxiety, seizures and respiratory arrest.

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ITDD – associated respiratory depression can be serious. Hence it is important for the supervising clinician to be aware of and manage all of a patient's CNS – active medications. Non-essential CNS medications may need to be eliminated. Communication with other treating physicians may be needed.

When starting intrathecal therapy, eliminate systemic opioids if possible or reduce them by at least 50% when elimination is not feasible. Start with low doses of ITDD drugs and escalate slowly. The goal of fine-tuning the opioid dose is to reach the lowest effective dose to minimise systemic side-effects. The most common side-effects of intrathecal opioid therapy - pruritis, nausea and vomiting, urinary retention and constipation frequently appear at the start of therapy, can usually be managed and generally resolved during the first three months of ITDD therapy.

Respiratory depression can be detected and treated if a patient is monitored following the start or restart of opioid therapy. Treatment cessation followed by refill or delayed refill and resumption of previous dosing can cause respiratory depression due to loss of opioid tolerance. Respiratory depression is an opioid dose-dependent phenomenon; the risk is also increased by co-morbidities such as obesity, illicit drug abuse and the use of other CNS depressants. Intrathecal therapy should be initiated/reinitiated at low doses with slow titration. All patients at initiation or reinitiating opioid therapy should be monitored in a fully equipped and staffed environment for at least 24 hours. Naloxone must be readily available.

Nursing staff should be educated about the unique monitoring requirements of patients being treated with ITDD.

Clinicians should familiarise themselves with the manufacturer's manual and with potential pump and catheter-related complications. Mechanical pump malfunction is uncommon and has declined with each generation of pumps. Pump stalls invariably result in under-dosing which becomes evident clinically as decreased efficacy or withdrawal symptoms. Most overdoses are caused by human error including programming error, use of wrong drug admixture or pocket fill. Incorrect refill may occur into the subcutaneous pocket with life threatening devastating consequences.

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Troublesome problems can occur with the pump pocket or the scar (e.g. the pump moving, the scar being thinned from within and the pump being uncomfortable). Some pumps may be MRI compatible and should be examined not less than 30 minutes after an MRI scan to ensure that the motor stall has re-started.

Catheters are the most vulnerable component of the system for damage or dislocation. Catheter complications include micro fracture, leaks, disconnection, breakage, kinks, partial occlusion, inflammatory mass, catheter migration. The symptoms of catheter problems are manifested as reduced efficacy, increased pain withdrawal symptoms and neurological dysfunction. The catheter may need to be revised, replaced or removed.

Development of an inflammatory mass (granuloma) at the tip of the catheter remains one of the most serious risks of ITDD. If an inflammatory mass is suspected the diagnostic work-up should include a complete patient history, neurological examination and a T1 weighted MRI performed with gadolinium.

In patients with cancer, neurological complications may occur as a result of tumour progression, vertebral collapse or obstruction of vascular supply, but may also be precipitated by bleeding or CSF leakage caused by the procedure. Unexpected paraparesis within 48 hours after dural puncture occurred in 5 out of a series of 201 patients.

Possible infections include meningitis, (bacterial, aseptic), catheter infections, implant site and wound infections.

Cerebrospinal fluid leaks, and post-dural puncture headaches have all been reported.

Guidelines should be in place to permit timely access to neuroradiological expertise and neurosurgical treatment if neural compression is suspected. Rarely, neurosurgical assessment will be required

Emergency algorithms for the detection, investigation and management of complications should be in place to support the surveillance of suspicious symptoms reported by the patient and their caregivers.

There must be clear pathways for dealing with complications, both in and out of hours. This will require agreed network arrangements. The patient's primary care team should be aware of potential complications, management plans, implanting team contacts and referral arrangements.

Issues with IT Pumps with peristaltic mechanism and drug mixtures

Peristaltic mechanism of action involves a small piece of silicone inner tube and a rotating roller. This is used in the Medtronic SynchroMed pump. Medtronic has issued a warning on use of drug mixtures in their intrathecal Pumps. Use of unapproved drugs/ mixtures with SynchroMed pumps can result in an increased risk of permanent motor stall and cessation of drug infusion. Approved drugs for infusion therapy with the Medtronic Synchromed systems include morphine sulphate, morphine hydrochloride, floxuridine, methotrexate or baclofen in solution. Based on data from Medtronic's Implantable Systems Performance Registry (ISPR), the overall failure rate of the SynchroMed II pump at 78 months post implant is 2.4% when used to dispense approved drugs, and 7.0% when used to dispense unapproved drugs¹⁷.

There has been variable reaction to this alert from the clinicians managing these patients. Clinical experience with these devices over many years does not seem to match with this alert (i.e. the risk seems very small) and it can easily be mitigated as patients are reviewed at regular intervals for pump refills and there is an alarm in the pump which warns of this possibility. This needs to be considered in the context of improved pain control offered by drug mixtures infused in the pump as recommended by the Polyanalgesic consensus conference in 2012 (Table 2). Benefits of combination therapy include mitigation of adverse effects associated with high drug doses due to the requirement for lower doses of each individual agent. Patient information sheet available from British Pain Society may be adjusted to include this point.¹⁸

10 Governance Arrangements

Medical Leadership and MDT Composition

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A minimum of two experienced pain medicine clinicians (usually FFPMRCA) that are experienced with assessing pain mechanisms and pain management in those with cancer indications. They must fully understand the indications, contraindications and perioperative management as well as all the potential other pain relief interventions (medical, surgical, neuromodulation, neuroablation etc.). They must be experienced in the management of medications at very high dose and in complex combinations.

These clinicians must be led by at least one senior and experienced clinician from the field with more than 5 years at consultant level or with extensive experience in this field. This team must be able to provide all the pain medicine related care needs of the patient throughout the process, including long term management of the ITDD (this care model may be shared care with local services).

Two clinicians able to undertake the interventional procedure (these may be the same FFPMRCA as above or neurosurgeons familiar with the technique working in collaboration with the above).

As well as the above, the ITDD MDT should include close and regular collaboration with senior palliative medicine consultants and their teams. Access to psychology and pain physiotherapy should be available. The decision should be made with input from: the patient and relatives (informed and shared decision making), the patient's local services (primary care, hospice etc.), cancer services (physician, surgeon, radiotherapy etc.) to ensure appropriate intervention and perioperative management, radiology.

A dedicated team of nurses, with a named nurse lead in the therapy should support, co-ordinate and ensure compliance with therapy transitional requirements (such as patient information documentation, anticoagulation needs, drug changes, support of ward staff etc.).

Experience of the pain consultants

As above: usually FFPMRCA can demonstrate that they are experienced with assessing pain mechanisms and pain management in those with cancer and complex pain. ITDD demands specialized knowledge and experience and thus the pain consultants involved should have specialist knowledge and expertise in

managing patients with ITDD. This experience is not widespread and so for now it will be clustered in specialized pain centres or networks that may involve other experienced specialist centres. They should have an established service, with proven track record of managing more than 5-10 implants per year for more than 5 years. The team should be a part of a Specialised PMC (on site or Operational Delivery Networked through contract with such a PMC)

Number of staff: as above

Specialties on site

An experienced pain medicine consultant and experienced named pain nurse should be on site during working hours and consultant available out of hours.

An experienced Acute and Chronic Pain Management Service, used to invasive procedures in complex patients, should provide 24 hour cover.

An appropriate support team from cancer services and Palliative Medicine should provide 24 hour cover.

Close working relationships and defined plan should be available for neurosurgery, though they do not need to be onsite as neurosurgical emergencies are rare.

ITU must be onsite.

Many of the patients are disabled and by definition distressed because of pain. As a consequence the Team must be able to come to the patient and all investigations and interventions should be onsite.

Access to Neurosurgery

The service must have established routine and emergency referral links to neurosurgery in the unlikely event of acute or chronic cord compression due to disease or granuloma. Rarely other complications such as development of pseudo-meningocele may require neurosurgical referral.

Emergency plans

Each patient will have a management plan that should include information about access to the ITDD team. Each ITDD team will ensure that there is 24 hour access to advice and if required urgent out of hours action if the issue cannot be deferred to office hours.

Patients with cancer related pain may require further access to Palliative Care. Once out of hospital, there should be an agreed patient care plan on how to manage patient and clinician concerns.

Emergency measure may require an A&E department and a hospital equipped with full critical care facilities including an intensive care unit.

Palliative Medicine

Once out of hospital, there should be an agreed patient care plan on how to manage patient and clinician concerns.

General Points

The infrastructure for ITDD is critical to reducing morbidity and mortality. This includes staffing, education and robust on-call arrangements with professionals trained and experienced both in the use and management of the implants and identification, investigation and management of complications of ITDDS. Much of that structure would be found in a specialised Pain Management Centre as defined in NHSE's Service Specification DO8.

The use of ITDD to treat intractable, chronic cancer pain should be part of treatment algorithms for chronic, severe pain and should be considered only when there is failure of more conservative treatment measures and when pain cannot be controlled with either high opioid doses or when unacceptable side-effects of high opioid doses/opioid tolerance develop. The number of patients in England is thought to be relatively small, currently around 50 new patients a year.

The treatment should be provided and directed by specialist MDTs in specialised Pain Management Centres. The specialist MDT is responsible for the organisation of follow-up arrangements that are safe and secure and that minimise morbidity and mortality. Causes of the later are largely avoidable and can be reduced by vigilance and team expertise in: careful patient evaluation, patient selection procedures, anaesthetic and surgical technique, trial of treatment, pump maintenance, refill procedures and patient follow-up with rapid recognition of complications and their

appropriate treatment. Appropriate Standard Operating Procedures (SOPs) and protocols should be developed for the treatment of respiratory depression, initiation and re-initiation of analgesic drugs after revision/cessation of intrathecal therapy etc.

Some preparations which are currently used do not have product licenses for ITDD. Guidance must be followed for the use of unlicensed drugs. The British Pain Society's 'The use of drugs beyond license in palliative care and pain management' guidelines provide useful general advice^x. Caution should be exercised on exceeding recommended doses, by the use of slow titration protocols.

It is the responsibility of the implanter and specialised pain management centre to keep adequate records of the implantation procedure and device. The patient should carry information indicating the make and model of any device, drugs within the pump and the current or last prescribed dose.

11 Mechanism for Funding

Intrathecal Pumps will be routinely funded provided this treatment is delivered in line with the Specialised Pain service specification and the requirements of this policy.

12 Audit Requirements

Accurate measures of pain intensity and its impact on function and quality of life i.e. Brief Pain Inventory, VAS and pain interference scores, EQ5D-5L (quality of life measure, pain related health function and well-being), Patient's Global Impression of change, Drugs, their concentration and doses pre procedure and as treatment is initiated and progresses (i.e. at outcome measure points). Such measures serve as a baseline measurement from which to determine the continuing impact of therapy.

Frequency and type of complications of complications both device and non - device related.

Number of patients assessed within three months of referrals for this treatment will be audited. Outcomes will be collected for cancer patients at 1 to 2 months initially for 6 months and every 3 to 4 months afterwards.

13 Documents which have informed this Policy

All relevant documents have been referenced in the text and included in the references section.

14 Links to other Policies

This policy follows the principles set out in the ethical framework that govern the commissioning of NHS healthcare and those policies dealing with the approach to experimental treatments and processes for the management of individual funding requests (IFR).

15 Date of Review

This policy will be reviewed in April 2017 unless information is received which indicates that the proposed review date should be brought forward or delayed.

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Appendix

Table 1. Algorithm for ITDD therapies in Neuropathic Pain (Published guidance on use of medications in ITDD (Polyanalgesic Consensus Conference 2012)

Please note: Ziconotide is not routinely commissioned by NHS England so should not be used

Line 1	Morphine	Ziconotide		Morphine + bupivacaine
Line 2	Hydromorphone	Hydromorphone+Bupivacaine or Hydromorphone+Clonidine		Morphine+Clonidine
Line 3	Clonidine	Ziconotide+Opioid	Fentanyl	Fentanyl+Bupivacaine or Fentanyl+Clonidine
Line 4	Opioid+Clonidine+Bupivacaine	Bupivacaine+Clonidine		
Line 5	Baclofen			

Table 2. Algorithm for ITDD therapies in Nociceptive Pain (Published guidance on use of medications in ITDD (Polyanalgesic Consensus Conference 2012)

Please note: Ziconotide is not routinely commissioned by NHS England so should not be used

Line 1	Morphine	Hydromorphone	Ziconotide	Fentanyl
Line 2	Morphine + Bupivacaine	Ziconotide+Opioid	Hydromorphone+Bupivacaine	Fentanyl + Bupivacaine
Line 3	Opioid + Clonidine			Sufentanil
Line 4	Opioid+Clonidine+Bupivacaine		Sufentanil+Bupivacaine or Clonidine	
Line 5	Sufentanil + Bupivacaine + Clonidine			

Table 3. Number of Pumps implanted per million population per annum in these countries

Pump type	Belgium	France	Holland	Germany	UK
Spasticity	34.6	1.72	4.5	13.12	9.7
Pain	18.3	-	1.5	figures not available	1.6
