Official Title of Study : Embrace TDD: Prospective, Multi-Center, Post-Market Study to Evaluate Intrathecal (IT) Morphine as an Alternative to Systemic Opioids for the Treatment of Chronic, Intractable, Non-Malignant Primary Back Pain with or without Leg Pain

NCT Number: NCT03761277

Date of Document: 26APR2021

Document Type: Study Protocol

Medtronic

Clinical Investigation Plan

Clinical Investigation Plan/Study Title	Embrace TDD: Prospective, Multi-Center, Post-Market Study to Evaluate Intrathecal (IT) Morphine as an Alternative to Systemic Opioids for the Treatment of Chronic, Intractable, Non-Malignant Primary Back Pain with or without Leg Pain
Clinical Investigation Plan Identifier	MDT18026
Study Product Name	Medtronic SynchroMed™ II infusion system and preservative-free morphine sulfate, USP (PFMS) and preservative free 0.9% Sodium Chloride Injections, USP (for dilution)
Sponsor/Local Sponsor	Medtronic Neuromodulation 7000 Central Avenue NE Minneapolis, MN 55432 USA 1-763-514-4000
Document Version	3.0
Version Date	26-Apr-2021

1. Investigator Statement

Participating investigators will be provided with a separate investigator agreement to document their obligations and commitment with respect to study conduct.

Table of Contents

[redacted]

2. Glossary

Acronym	Definition
ADE	Adverse Device Effect
AE	Adverse Event
BL	Baseline Visit
[redacted]	[redacted]
CEC	Clinical Event Committee
CFR	Code of Federal Regulation
CIP	Clinical Investigation Plan (“Protocol”)
CMM	Conventional Medical Management
CNS	Central Nervous System
CRF	Case Report Form
CSF	Cerebral Spinal Fluid
DD	Device Deficiency
eCRF	Electronic Case Report Form
[redacted]	[redacted]
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IC / ICF	Informed Consent / Informed Consent Form
ICH-E6	International Conference of Harmonization (ICH) Guideline for Good Clinical Practice (ICH-E6)
ICMJE	International Committee of Medical Journal Editors
IFP	Information for Prescribers
IRB	Institutional Review Board

Acronym	Definition
ISO	International Organization for Standardization
IT	Intrathecal
LTFU	Lost-To-Follow-Up
MAT	Medication Assisted Treatment
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
MME	Morphine Milligram Equivalents
NDA	New Drug Application
NOSE	Numerical Opioid Side Effect Assessment Tool
NPU	Neuro Programmer Upload
[redacted]	[redacted]
PACC	Polyanalgesic Consensus Conference
PFMS	Preservative-Free Morphine Sulfate
[redacted]	[redacted]
PI	Principal Investigator
PMA	Pre-Market Application
RCT	Randomized Controlled Trial
RDC	Remote Data Capture
RPA	Returned Product Analysis
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SUD	Substance Use Disorder

Acronym	Definition
TDD	Targeted Drug Delivery
US	United States [of America]
USP	Unites States Pharmacopoeia
VAS	Visual Analog Scale

3. Synopsis

Title	Embrace TDD: Prospective, Multi-Center, Post Market Study to Evaluate Intrathecal (IT) Morphine as an Alternative Systemic Opioids for the Treatment of Chronic, Intractable, Non-Malignant Primary Back Pain with or without Leg Pain
Clinical Study Type	Post-Market Interventional
Product Name	Medtronic SynchroMed™ II infusion system: The Medtronic SynchroMed II infusion system consists of an implanted infusion pump and catheter, and external components, a clinician programmer, refill and catheter access port kits, the Personal Therapy Manager® (myPTM™). SynchroMed II infusion system components that become commercially available after the commencement of this study may also be used in addition to, or in lieu of, the currently available components. The pharmacological agent used in the study is limited to preservative-free morphine sulfate, USP (PFMS) and preservative free 0.9% Sodium Chloride Injections, USP (for dilution).
Sponsor	Medtronic Neuromodulation 7000 Central Avenue NE Minneapolis, MN 55432 USA 1-763-514-4000
Indication Under Investigation	Use of Intrathecal Drug Delivery System (IDDS) to manage subjects with chronic, intractable, non-malignant primary back pain with or without leg pain.
Investigation Purpose	To assess pain control and opioid-related side effects following a route of delivery change from systemic opioid therapy to IT morphine therapy.

<table>
<tr><td>Product Status</td><td>All Medtronic products used in this study are commercially available in the United States and will be used within the specifications of product labeling.
The pharmacological agent used in the study is limited PFMS and preservative free 0.9% Sodium Chloride Injections, USP (for dilution).
None of the Medtronic products used in this study are investigational.</td></tr>
<tr><td>Primary Objective</td><td>To characterize the proportion of subjects with Clinical Success at the 6-Month Visit based on changes in pain intensity using the Visual Analog Scale (VAS) and changes in opioid-related side effects using the Numerical Opioid Side Effect (NOSE) Assessment Tool.
Clinical Success is defined as any of the following (refer to grid below with matching numbers):
1) Reduced opioid-related side effects with equal pain
2) Reduced pain with equal opioid-related side effects
3) Reduced pain and reduced opioid-related side effects

Criteria for Clinical Success
<table>
<tr><td colspan="3" rowspan="2">Change
from Baseline
to the 6-Month Visit</td><td colspan="3">Opioid-Related Side Effects
(NOSE)</td></tr>
<tr><td>≥20%
Increase</td><td>< ±20%
Change</td><td>≥20%
Reduction</td></tr>
<tr><td colspan="3"></td><td>Worse</td><td>Equal</td><td>Better</td></tr>
<tr><td rowspan="3">Pain Intensity (VAS)</td><td>≥20%
Increase</td><td>Worse</td><td></td><td></td><td></td></tr>
<tr><td>< ±20%
Change</td><td>Equal</td><td></td><td></td><td>1</td></tr>
<tr><td>≥20%
Reduction</td><td>Better</td><td></td><td>2</td><td>3</td></tr>
</table>
</td></tr>
<tr><td>Secondary Objectives</td><td>1. To demonstrate pain intensity scores (VAS) at the 6-Month Visit is non-inferior to VAS at Baseline
2. To characterize the change in opioid-related side effect scores (NOSE) from Baseline to the 6-Month Visit
3. To characterize the proportion of subjects who eliminate systemic opioids through the 6-Month Visit</td></tr>
</table>

[redacted]	[redacted]
Safety Assessments	To characterize all systemic opioid weaning-related, device-related, IT drug-related, and procedure-related adverse events (AEs), all serious adverse events (SAEs) (regardless of relatedness), and device deficiencies (DD) for all subjects from enrollment until the subject exits.
Study Design	The Embrace TDD study is a prospective, multi-center, post-market study. Subjects with chronic, intractable non-malignant primary back pain with or without leg pain will be enrolled in the study and will be required to attend a minimum of 7 in-office visits which include: Baseline, Intrathecal Trial, Implant, Post-Op, 1-Month, 3-Month, and 6-Month. Participation in the study can last up to 18 months for a subject depending on weaning duration and follow-up requirements in place prior to CIP V3.0 implementation.
Sample Size	93 subjects have been enrolled into the study with the intent to achieve approximately 67 implanted subjects and 50 evaluable subjects at the 6-Month Visit. The sample size of 50 evaluable subjects was chosen to assure acceptable levels of precision for estimation of the primary objective of Clinical Success and provide adequate power to test the secondary objective related to pain score.
Inclusion/Exclusion Criteria	<u>Inclusion Criteria</u> A potential subject may be included for participation in the study if the subject has/is: 1. Willing and able to provide a signed and dated (Medtronic and Institutional Review Board (IRB) approved) Informed Consent Form (ICF) and Health Insurance Portability and Accountability Act

	(HIPAA) Authorization Form prior to any study procedures being performed 2. A candidate per labeling for the IDDS 3. A diagnosis of chronic, intractable non-malignant, primary back pain with or without leg, pain treatable with the IDDS 4. Current daily systemic opioid dose of > 0 and ≤ 120 Morphine Milligram Equivalents (MME) 5. A Visual Analogue Scale (VAS) of ≥50 mm for pain intensity at the Baseline Visit and/or a Numerical Opioid Side Effect (NOSE) Assessment Tool ≥40 for intolerable side effects at the Baseline Visit 6. Psychological evaluation or investigator assessment of patient psychological suitability for study participation 7. Has an MRI or CT prior to enrollment verifying patent spinal canal and no clinical change in status since last imaging 8. At least 18 years old at time of enrollment 9. Willing and able to attend visits and comply with the study protocol 10. Male or non-pregnant, non-lactating female. Females must be post-menopausal or surgically sterile; or be utilizing a medically acceptable form of birth control (i.e. a hormonal contraceptive, intra-uterine device, diaphragm with spermicide, or condom with spermicide) for the duration of the study <u>Exclusion Criteria</u> A potential subject will be excluded from participating in the study if the subject has/is: 1. Previously trialed or implanted with an IDDS 2. Concomitant stimulation device implanted for the treatment of pain 3. Any ongoing health condition that would be expected to interfere with pain and/or quality of life ratings (i.e. active malignancy, other painful conditions not treatable with IT therapy, etc.) 4. Psychological or other health conditions, financial and/or legal concerns that would interfere with the subject's ability to fulfill the requirements of the protocol as per the investigator's discretion 5. Substance Use Disorder (SUD) within the last 2 years or current Medication Assisted Treatment (MAT) for substance use disorder 6. Currently using cannabinoids or illicit drugs 7. History of allergy or significant adverse reaction to morphine per investigator discretion 8. Currently participating or plans to participate in another investigational study unless written approval is provided by Medtronic Study Team

Study Procedures and Assessments	Subjects will be considered enrolled at the time they sign the informed consent. Subjects will then be required to wean off all systemic opioid medications within 5 months (with a minimum of a 7-day opioid holiday) prior to initiation of IT therapy. Scheduled Visits will include the following: Baseline, IT Trial, Implant, Post-Op, 1-Month, 3-Month, and 6-Month. The following assessments / data will be collected during the study: a. IT PFMS Dose b. VAS for pain intensity c. NOSE for opioid-related side effects [redacted] j. Pain Medications k. Adverse Events (AE) l. Device Deficiencies (DD)
Statistics	For the primary objective of Clinical Success, the proportion of subjects with Clinical Success at the 6-Month Visit and its two-sided exact binomial 95% confidence interval (CI) will be reported. For the secondary objective of pain intensity score, a non-inferiority t-test will be applied; if non-inferiority is met, a superiority t-test will be followed. The pain scores at both the Baseline and 6-Month Visits as well as the change from Baseline to the 6-Month Visit will be reported. For the secondary objective of NOSE score, descriptive statistics (mean and standard deviation, etc.) will be used to report the NOSE score at Baseline and the 6-Month Visits, as well as the change from Baseline to the 6-Month Visit. For the secondary objective of proportion of subjects who eliminate systemic opioids, the proportion and its exact binomial two-sided 95% CI will be reported. [redacted] Adverse events and device deficiencies will be summarized using summary tables displaying the frequency, percentage, relatedness and seriousness.

4. Introduction

4.1 Background

Though morphine use has a documented history going back centuries, intrathecal (IT) use was first reported in 1979 as a treatment for cancer pain.[1] Anecdotal reports and publications of single-patient or small cohort usage increased the use of IT morphine as a treatment for both malignant and non-malignant pain over the next few years. A 1981 publication reported the first use of an implanted pump, the fixed-rate Infusaid Model 400, for chronic infusion of morphine as a treatment for pain. [2] Continued use, the recognized need, and pressure from patient advocacy groups prompted the Food and Drug Administration (FDA) to publish a request to industry for applications seeking approval for an effective treatment for cancer pain. In July 1991, Hikma Maple received New Drug Application (NDA) (N018565) approval for Infumorph (10 mg/mL and 25 mg/mL preservative-free morphine sulfate).

In March 1988, Medtronic, Inc. obtained Pre-Market Application (PMA) (P860004) approval for SynchroMed for the delivery of chemotherapeutic agents (intravascular floxuridine [FUDR], doxorubicin hydrochloride (Adriamycin), bacteriostatic water, physiological saline and/or heparin). In July 1991, PMA supplement P860004/S001, originally filed in August 1987, was approved expanding the SynchroMed indication to include IT administration of preservative-free morphine sulfate (PFMS) for the treatment of chronic intractable pain of malignant origin. In October 1991, the SynchroMed indication was expanded to include chronic intractable pain of non-malignant origin as well. Since the time of these original approvals, evidence-based medicine has emerged as a discipline for evaluating safety and efficacy, creating the need for a high level of evidence to ensure coverage and use. Since approval, the management of IT opioids has evolved and best practices for managing patients with chronic pain have been developed. IT drug delivery was originally developed to be a more efficient and efficacious method of delivering medication directly to the site of action, reducing the amount of drug needed. This idea suggests that targeted drug delivery (TDD) is more effective (e.g., smaller doses, equianalgesia, reduced side effects) than systemic drug administration of opioids in the treatment of chronic non-malignant pain.

Clinical evidence comparing systemic opioid administration to intrathecal administration has been collected in small scale studies and in a single larger randomized controlled trial (RCT) for malignant pain. [3] Given the current opioid epidemic and ongoing pain management crisis, it's more important than ever for patients suffering from chronic pain to have access to proven alternatives. Clinical evidence specific to non-malignant pain and IT morphine sulfate is needed. This study is intended to augment existing medical evidence specific to the approved indication of treatment for chronic intractable pain of non-malignant origin. Current guidelines regarding patient selection, trialing, implant, and dosing for this therapy will be followed, allowing for selection and treatment of subjects in a manner similar to standard practice. TDD with IT morphine may provide an opportunity to reduce drug dosing requirements, minimize opioid side-effects, and provide equivalent or improved analgesia.

In addition to an assessment of pain relief, this study will evaluate changes with regard to commonly accepted side effects related to opioid use, including sleep disturbances, sedation, clouded thinking, constipation, and others.

4.1.1 Preclinical Data

IT morphine use in the treatment of malignant pain dates back to the late 1970's, with chronic infusion being used since the early 1980's. Laboratory studies (in vitro and in vivo) supported this initial clinical use of IT morphine and the greater than 30 years of use as a therapy for chronic pain subjects preclude the need for additional preclinical data supporting this therapy. One noted exception, however, is the dose/concentration-dependent development of catheter tip inflammatory mass formation with chronic IT delivery of morphine sulfate.[5–7] Animal models have been developed and study results indicate the causal effect of IT morphine on inflammatory mass formation.[7] Clinical experience supports these results and mitigation factors have been incorporated into clinical practice. Mitigation practices currently in place include the use of lower concentrations and doses of IT morphine to reduce the risk of inflammatory mass formation, and lower catheter tip placement in the spinal column to minimize clinical impact should an inflammatory mass develop.

As this is a post-market study using only commercially available products, a separate Investigator Brochure is not required. The Technical Manuals will be provided separately.

4.1.2 Clinical Data

The use of SynchroMed along with IT morphine for the treatment of chronic, intractable pain has been reported in published scientific literature; however, the level of quality (based on guidelines from the Center for Evidence-Based Medicine in Oxford)[a] is limited.

IT morphine has been used clinically since 1979 and SynchroMed has been approved for use in chronic non-malignant pain since 1991. Over these years of clinical use, numerous publications on safety, drug efficacy, and device effectiveness have been published. To date, however, only four Oxford Level 1 manuscripts have been published supporting the use of the SynchroMed for the treatment of pain; three applicable to Prialt® (ziconotide) and one applicable to malignant pain (with morphine).[3,9–11]

In 2002, results of the Medtronic-sponsored RCT comparing comprehensive medical management to implantable drug delivery for treatment of malignant-related pain were published.[3] Prior to this study, all available data were from small, open-label, cohort studies. This study was able to demonstrate that TDD improved clinical success in pain control, reduced pain, significantly relieved common drug toxicities, with a trend toward improved survival in subjects with refractory malignant pain. In this study,

[a] OCEBM Levels of Evidence Working Group*. "The Oxford 2011 Levels of Evidence". Oxford Centre for Evidence-Based Medicine. http://www.cebm.net/index.aspx?o=5653

IT drug use was limited to opioids (morphine or hydromorphone, as this was an international study) during the first 4 weeks only and then opened to other medications as necessary to treat pain. Endpoint assessments were completed at 4 weeks and showed improvement in pain visual analog scale (VAS) scores for both Comprehensive Medical Management (CMM) and the Implantable Drug Delivery System (IDDS) with a non-statistically significant greater improvement in the TDD group. Improvement in toxicity scores was statistically significantly greater in the TDD group.

Results of 3 prospective 3-year follow-up studies of subjects treated with low-dose intrathecal opioids were published in 2012, 2015, and 2016.[12,13,15] These studies demonstrated that conversion to IT opioids, discontinuation of systemic opioid use, and maintenance on low doses of IT opioids can effectively be used to treat chronic pain. In 2012, twelve experienced pain management practitioners met to identify and publish a paper discussing best practices in three areas related to safe IT therapy for pain: safety and monitoring, patient and device management, and patient selection and trialing, the results of which were published in 2014.[20] They concluded that intrathecal drug delivery is a valuable alternative drug delivery system for many patients with severe chronic or end-of-life pain. They also noted that while device-related complications (mostly with catheters) and surgical-site infections can occur, the main therapy-related safety issues associated with IT drug delivery arise primarily with inadequate patient monitoring (e.g., respiratory depression), inflammatory mass (e.g., high doses and concentrations of opioids), wound healing, dosing errors (e.g., medication concentration and pump programming), pump fills or refills (e.g., pocket fills), and interaction with concomitant systemic medications (e.g., opioids and benzodiazepines). They stated that many of the reported adverse events and complications of IT drug delivery can be prevented by adequate clinician training, implementation of best practices, and experience. In adopting the therapy, patients must be apprised of its risks and benefits. Physicians and patients must partner to achieve both safety and effectiveness.

In 2000 a Polyanalgesic Consensus Conference (PACC) was convened for the first time to review existing data specific to TDD and evaluate medical evidence gaps. The PACC convened most recently in 2014 to address IT therapy deficiencies and innovations that occurred since the previous PACC convened in 2012. Three companion pieces were published in 2017 including best practices and guidelines, improving safety and mitigating risks, and intrathecal trialing.[17–19] The PACC 2017 recommends the use of on-label drugs, including morphine, as first-line therapy, and indicates this placement remains supported by available clinical data. Clinical studies, however, are primarily retrospective or single-center studies, underscoring the need for higher quality clinical data. The current study is intended to collect prospective multicenter medical evidence supporting the existing indication and medically accepted uses of IT morphine and SynchroMed II for chronic pain.

4.2 Purpose

The purpose of this study is to assess pain control and opioid-related side effects following a route of delivery change from systemic opioid therapy to IT morphine therapy.

4.3 Regulatory Study Classification

This on-label, post-market clinical study will be using the SynchroMed II infusion system with preservative-free morphine sulfate, USP (PFMS) and preservative free 0.9% Sodium Chloride Injections, USP (for dilution). The study will be conducted at approximately 15 sites in the United States and has enrolled 93 subjects with chronic, intractable primary back pain with or without leg pain. The study will be conducted in accordance with this protocol, the ethical principles that have their origin in the Declaration of Helsinki, all applicable regulatory requirements (21 Code of Federal Regulations [CFR] §50 Protection of Human Subjects, 21CFR§54 Financial Disclosure by Clinical Investigators, and 21CFR§56 Institutional Review Boards [IRB], 21CFR§803 Medical Device Reporting), and International Council for Harmonization (ICH GCP E6). This study will be posted on ClinicalTrials.gov as part of Medtronic's commitment to full disclosure for ongoing studies that meet the requirements for public posting.

Documentation for this study will be produced and maintained to ensure that a complete history of the study exists. Documents created for this study, including all versions of original documents, will be identifiable and appropriately stored to assure control and traceability of data related to this study.

5. Objectives and/or Endpoints

5.1 Objectives

5.1.1 Primary Objective

To characterize the proportion of subjects with Clinical Success at the 6-Month Visit based on changes in pain intensity using the Visual Analog Scale (VAS) and changes in opioid-related side effects using the Numerical Opioid Side Effect (NOSE) Assessment Tool.

Clinical Success is defined as any of the following *(refer to grid below with matching numbers)*:

1) Reduced opioid-related side effects with equal pain
2) Reduced pain with equal opioid-related side effects
3) Reduced pain and reduced opioid-related side effects

Criteria for Clinical Success

Change from Baseline to the 6-Month Visit			Opioid-Related Side Effects Score (NOSE)		
			≥20% Increase	< ±20% Change	≥20% Reduction
			Worse	Equal	Better
Pain Intensity (VAS)	≥20% Increase	Worse			
	< ±20% Change	Equal			**1**
	≥20% Reduction	Better		**2**	**3**

5.1.2 Secondary Objectives

1. To demonstrate pain intensity scores (VAS) at the 6-Month Visit is non-inferior to VAS at Baseline
2. To characterize the change in opioid-related side effect scores (NOSE) from Baseline to the 6-Month Visit
3. To characterize the proportion of subjects who eliminate systemic opioids through the 6-Month Visit

[redacted]

5.1.4 Safety Assessment

To characterize all systemic opioid weaning-related, device-related, IT drug-related, and procedure-related adverse events (AEs), all serious adverse events (SAEs) (regardless of relatedness), and device deficiencies (DD) for all subjects from enrollment until the subject exits.

6. Study Design

This is a prospective, multi-center, post market study with commercially available products to evaluate the pain control and opioid-related side effects following a route of delivery change from systemic opioid therapy to IT morphine therapy in subjects with chronic, intractable, non-malignant primary back pain with or without leg pain. The study will be conducted at approximately 15 study sites in the United States.

Patients that meet all inclusion criteria, do not meet any exclusion criteria, and provide written Informed Consent Form (ICF)/Health Insurance Portability and Accountability Act (HIPAA) Authorization Form will be enrolled in the study. Medtronic products used in this study will be used within the specifications of product labeling. The pharmacological agent used in the study is limited to PFMS and preservative free 0.9% Sodium Chloride Injections, USP (for dilution).

Ninety-three subjects have been enrolled into the study with the intent to achieve approximately 67 implanted subjects and at least 50 evaluable subjects at the 6-Month Visit. All subjects implanted with the IDDS will be followed through their required study exit visit. The study sample size accounts for the expected attrition anticipated throughout the duration of the study, and therefore, subjects who are exited or discontinue will not be replaced.

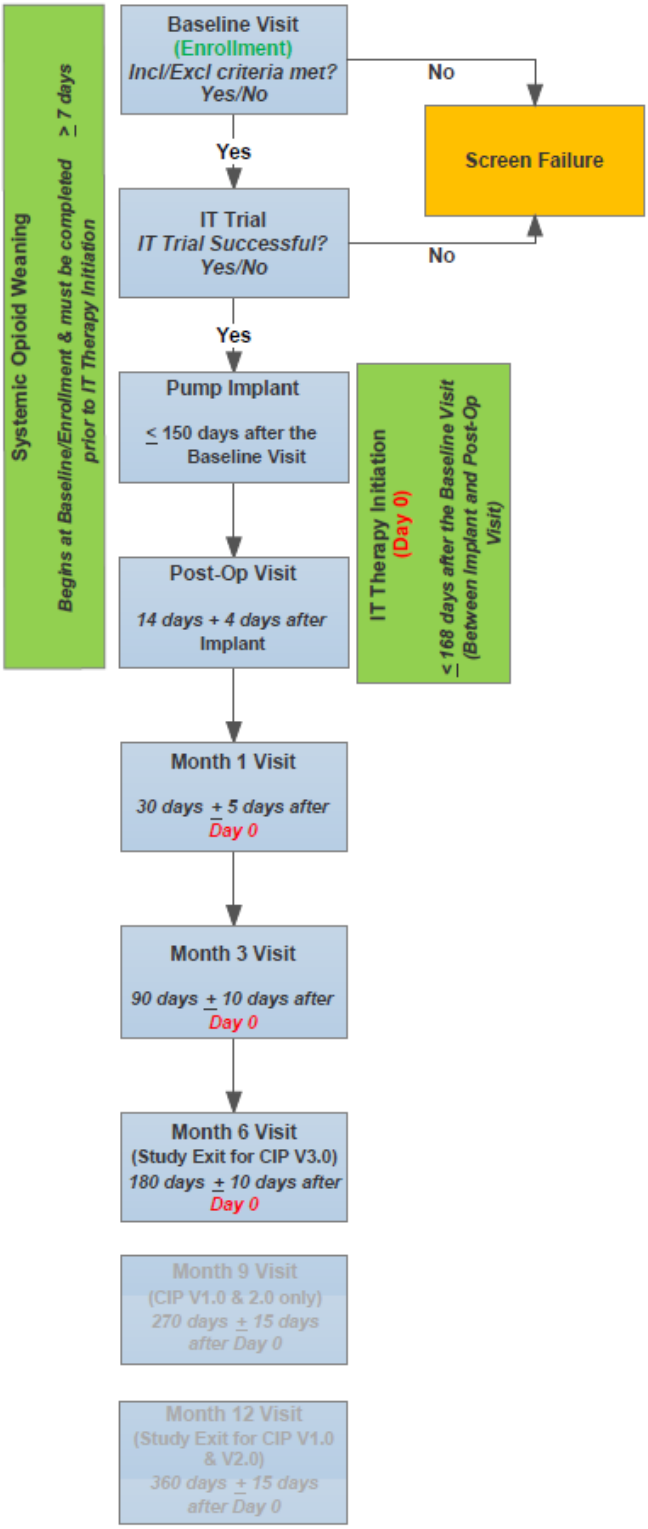
If an activated site does not enroll any subject within three months of activation, Medtronic may choose to terminate their participation in the study and move forward with another potential study site to ensure sufficient subject enrollments.

To ensure a distribution of data and minimize center bias in study results for analysis of the primary and secondary objectives, the maximum number of subjects that may be enrolled at a single site is 15, with Medtronic pre-approval required for additional enrollments.

Selection of subjects, treatment of subjects, and evaluation of study data are potential sources of bias. Potential sources of bias that may be encountered in this study have been considered and minimized by careful study design. Methods incorporated in the study design to minimize potential bias include (but are not limited to) the following:

- Subjects will be screened to confirm eligibility for enrollment with defined inclusion/exclusion criteria
- Subject demographics will be collected to assess possible characteristics that may influence endpoints
- To ensure widespread distribution and data among centers, the maximum number of subjects that may be enrolled at a single site is 15, with Medtronic pre-approval required for additional enrollments. Additionally, centers will each be encouraged to enroll at least 5 subjects
- A statistical analysis plan will be developed prior to analyzing data which will document pre-specified analysis and analysis methods
- All study site personnel and Medtronic personnel will be trained on their respective aspects of the study using standardized training materials
- All study site personnel will be trained on and required to follow the Clinical Investigation Plan (CIP)
- A Clinical Events Committee (CEC) will be utilized to adjudicate the relatedness and seriousness classifications of all reportable AEs and deaths

Figure 1: Embrace TDD Study Visit Flowchart



6.1 Duration

Enrollment is defined as the date the subject first signs the study informed consent/HIPAA form. Enrolled subjects will be required to attend a minimum of 7 in-office visits. Study completion for each subject is defined as the conclusion of the 6-Month Visit (Study Exit). Each subject's participation in the study is expected to last approximately 11 months from the date of enrollment to completion of the 6-Month Visit.

The duration of time needed to enroll 93 subjects in the study was 2 years and 1 month. The overall study duration, from first subject enrollment to last subject visit, is expected to last approximately 3 years. Study completion is defined as the approval of the Final Study Report and closure of all study sites.

6.2 Rationale

Information from available literature (Section 4.1) supports the need for clinical studies to assess IT morphine as an alternative route of delivery and its impact on efficacy and safety outcomes. Many chronic pain patients may not be achieving adequate pain management with systemic agents, are at higher risk for dose-limiting side effects or can become tolerant to opioids over time. Additionally, by changing the route of delivery, there is potential to eliminate the need for adjunctive chronic systemic opioids, which may lead to a reduction of opioid-related systemic side effects.

Studies of systemic opioids indicate an increase in overdose risk as a function of increased daily dose. Dunn et al. reported that adults who started use of opioid analgesics for a pain condition and were receiving 100 mg per day or more of an average prescribed daily opioid dose had an 8.9-fold increase in overdose risk compared with subjects receiving 1 to 20 mg/day of these medications. Furthermore, subjects receiving 50 to 99 mg/day had a 3.7-fold increase in overdose risk compared with subjects in the lowest-dose group.[24]

A demonstration of overall benefit is required to justify a route of delivery change when a more invasive therapy is proposed. A combined endpoint of clinical success was chosen for this study to assess the overall benefit of the therapy. Clinical success for this study is the improvement in either pain or opioid-related side effects, at the individual subject level. Smith et al[3] reported the use of a combination endpoint with malignant pain subjects, with clinical success defined as a ≥20% reduction in VAS, or equal pain scores with ≥20% reduction in opioid-related side effects.

This study is designed to establish medical evidence that intrathecal morphine is an effective alternative for the management of chronic intractable pain and implementing an opioid wean and holiday results in positive outcomes.

7. Product Description

7.1 General

The Medtronic SynchroMed II infusion system and related components and accessories used in this study are commercially available. SynchroMed II infusion system components that are commercially available after commencement of this study may also be used in addition to, or in lieu of the currently available components.

The Medtronic SynchroMed II infusion system will be the only implantable system allowed in this study and will be used in accordance with the product labeling.

The pharmacological agent used in the study is limited to PFMS and preservative free 0.9% Sodium Chloride Injections, USP (for dilution).

Table 1: Study Products

	Medtronic Product	Model
Implantable Components	Pump	8637-20 SynchroMed™ II Pump 8637-40 SynchroMed™ II Pump
	Catheters	8780 Ascenda™ Intrathecal Catheter Kit 8781 Ascenda™ Intrathecal Catheter Kit 8782 Ascenda™ Intrathecal Catheter Spinal Segment Revision Kit 8784 Ascenda™ Intrathecal Catheter Pump Segment Revision Kit
	Catheter Accessory Kits	8785 Catheter Accessory Kit 8786 Needle Catheter, Short 8787 Needle Catheter, Long 8591-38 Catheter Passer 8591-60 Catheter Passer
	Refill Kit and Catheter Access Port Kit	8540 Catheter Access Port Kit 8551 Refill Kit 8555 Refill Kit
	Clinician Devices	CT900 Clinician Programmer (tablet) A810 SynchroMed II Clinician Programmer Application A901 Communicator Manager Application A902 Patient Data Service Application 8880T2 Communicator
	Patient Devices/Accessories	TH90T01 Personal Therapy Manager (myPTM™) TM90 Communicator HH90 Handset with A820 myPTM Application software

SynchroMed II infusion system Manuals are provided with the products and are also available electronically at http://manuals.medtronic.com/manuals/main/region.

7.2 Dosage Form and Route of Administration

Sites will utilize PFMS per the investigator's standard of care and in accordance with the IT PFMS dosing goals and IT PFMS dose adjustment parameters outlined in Section 10.13.

Preservative-free (0.9%) Sodium Chloride Injection for IT administration: may be used to dilute PFMS to the desired concentration or to fill the pump reservoir prior to introduction of PFMS or if PFMS is removed and no other drug is placed in the pump.

7.3 Manufacturer

The SynchroMed II infusion system is manufactured by Medtronic, Inc. with operational headquarters in Minneapolis, Minnesota 55432-5604, USA.

7.4 Packaging

All Medtronic devices that will be used in this study are commercially available for IT drug delivery as an aid in the management of chronic, intractable pain. The devices specified in Section 7.1 will be shipped in their commercially available form, which includes packaging and labeling. Only commercial device products with commercial labeling will be used in this study. Each study site will order devices through their standard ordering processes and should follow their own accountability and storage processes, in accordance with the product labeling and their institution's policies and procedures.

The pharmacological agent used in this study will be PFMS. Each study site will order drug through their standard ordering processes and should follow their own accountability and storage processes, in accordance with the product labeling and their institution's policies and procedures, since these are controlled substances. No additional product accountability logs will be required for tracking these commercially available products in this study. All Medtronic device product manuals can be found electronically at http://manuals.medtronic.com/manuals/main/region.

7.5 Intended Population

The SynchroMed II infusion system is utilized in this study to deliver PFMS intrathecally in the treatment of patients with chronic, intractable, non-malignant, primary back pain with or without leg pain who are experiencing inadequate pain relief and/or intolerable side effects with their systemic opioid therapy.

7.6 Product Use

The Medtronic SynchroMed II infusion system and related components and accessories are commercially available in the United States and shall be used in accordance with commercial labeling. Exposure to the Medtronic study product is considered to occur from the time the subject is first exposed to the IDDS (during the device implant visit) until either the IDDS is explanted or the subject discontinues from the study.

7.7 Product Training Materials

Only investigators who are trained and experienced in implanting the SynchroMed II infusion system will perform the pump trial, pump implant, and pump refill procedures required for this clinical study. All study site personnel participating in the study will be required to complete all study-specific training as required in the Study Training Plan and have proper delegation by the Principal Investigator (PI) on the Delegation of Authority Log maintained at the site.

7.8 Product Receipt and Tracking

This is a post-market study and the Medtronic SynchroMed II infusion system and PFMS used in this study are commercially available. As this is a post-market study, study center personnel will order devices through their standard procedure for acquiring commercial product and site personnel should follow their standard procedures for tracking and managing supplies.

7.9 Product Storage

Sites should ensure proper storage conditions and record keeping for all products used in the study, per applicable labeling and per their institutions' policies and procedures.

7.10 Product Return

To fully evaluate product performance, Medtronic requests that explanted Medtronic products be returned for complete analysis. Therefore, Medtronic implantable products, explanted or opened, must be returned to Medtronic for analysis when permissible by local laws and regulations, when those products are no longer in use, regardless of reason for explants or removal from use. Furthermore, Medtronic requests the return of explanted product from non-clinical sources, such as funeral homes, and will assume responsibility for storage and disposal of the product once received.

Mailer kits with prepaid US postage are available for use within the United States to send explanted devices to Medtronic Neuromodulation Returned Product Analysis Lab. These mailers are sized to accommodate the devices from a single subject and are designed to meet postal regulations for mailing biohazardous materials.

Please contact your local Medtronic representative to obtain a Returned Product Mailer Kit or to obtain instructions on returning products to Medtronic.

All drugs utilized in this study must be disposed of as required by local laws and each site's institutional policies and procedures.

Returned Product Analysis

Devices that are returned to Medtronic, Inc. are analyzed via a Returned Product Analysis (RPA) system following specific protocols to identify root cause for failure or deficiency. When programming data are available on the IDDS, an expected longevity can be determined, and battery depletion (where applicable) can be identified as normal or premature. Upon PI request, a summary report of Medtronic's findings will be provided to the PI after analysis completion.

7.11 Product Accountability

Product accountability is not required since the Medtronic SynchroMed II infusion system and PFMS used in this study are commercially available. All devices and drugs used during the study will be purchased by sites through their standard procedure for acquiring commercial product and maintained per the applicable product labeling and the institutions' standard procedures.

8. Study Site Requirements

All investigator and site selection activities were complete prior to implementation of CIP V3.0.

8.1 Investigator/Investigation Site Selection

All investigators managing the subject's chronic pain must be qualified practitioners and experienced in the diagnosis and treatment of subjects with chronic pain. All PIs or appropriately delegated Sub-Investigators must be experienced and/or trained in the implant and management of the Medtronic SynchroMed II infusion system.

The role of the principal investigator is to implement and manage the day-to-day conduct of the clinical investigation as well as ensure data integrity and the rights, safety and well-being of the subjects involved in the clinical investigation.

The principal investigator shall:

- Be qualified by education, training, and experience to assume responsibility for the proper conduct of the clinical investigation
- Be experienced in the field of application and training in the use of the Medtronic SynchroMed II infusion system

- Disclose potential conflicts of interest, including financial, that interfere with the conduct of the clinical investigation or interpretation of results
- Be able to demonstrate that the proposed investigational study site:
  - Has the required number of eligible subjects needed within the recruitment period
  - Has one or more qualified investigators, a qualified investigational study site team and adequate facilities for the foreseen duration of the clinical investigation

Study site personnel training will be completed and documented prior to participation in this study.

8.2 Study Site Activation

During the activation process (prior to subject enrollment), Medtronic will train study site personnel according to their delegated tasks and in accordance with the study training plan. If new members join the study site team, they will receive training on the applicable study requirements relevant to their role before contributing to the study.

Prior to performing study related activities, all regulatory requirements shall be fulfilled, including, but not limited to the following:

- IRB approval of CIP and site-specific ICF
- Fully executed Clinical Trial Agreement
- Financial disclosure
- Curriculum Vitae of investigators and key members of the investigation study site team
- Documentation of delegated tasks
- Documentation of study training
- Additional requirements imposed by the IRB shall be followed, if appropriate.

Medtronic will provide each study site with documentation of study site/investigator readiness; this letter must be received prior to performing study related activities.

9. Selection of Subjects

9.1 Study Population

Patients with chronic, intractable, non-malignant primary back pain with or without leg pain, are the intended study population.

9.2 Subject Enrollment

93 subjects with chronic, intractable, non-malignant primary back pain with or without leg pain that met eligibility criteria and provided written informed consent/HIPAA were enrolled in this study. Subjects were enrolled at 16 study sites in the US, with no more than 15 subjects enrolled at each site, unless the site received pre-approval from Medtronic for additional enrollments.

9.3 Inclusion Criteria

A potential subject may be included for participation in the study if the subject has/is:

1. Willing and able to provide a signed and dated (Medtronic and Institutional Review Board (IRB) approved) Informed Consent Form (ICF) and Health Insurance Portability and Accountability Act (HIPAA) Authorization Form prior to any study procedures being performed
2. A candidate per labeling for the IDDS
3. A diagnosis of chronic, intractable, non-malignant primary back pain with or without leg pain, treatable with the IDDS
4. Current daily systemic opioid dose of >0 and ≤ 120 Morphine Milligram Equivalents (MME)
5. A Visual Analogue Scale (VAS) of ≥50 mm for pain intensity at the Baseline Visit and/or a Numerical Opioid Side Effect (NOSE) Assessment Tool ≥40 for intolerable side effects at the Baseline Visit
6. Psychological evaluation or investigator assessment of patient psychological suitability for study participation
7. Has an MRI or CT prior to enrollment verifying patent spinal canal and no clinical change in status since last imaging
8. At least 18 years old at time of enrollment
9. Willing and able to attend visits and comply with the study protocol
10. Male or non-pregnant, non-lactating female. Females must be post-menopausal or surgically sterile; or be utilizing a medically acceptable form of birth control (i.e. a hormonal contraceptive, intra-uterine device, diaphragm with spermicide, or condom with spermicide) for the duration of the study

9.4 Exclusion Criteria

A potential subject will be excluded from participating in the study if the subject has/is:

1. Previously trialed or implanted with an IDDS
2. Concomitant stimulation device implanted for the treatment of pain
3. Any ongoing health condition that would be expected to interfere with pain and/or quality of life ratings (i.e. active malignancy, other painful conditions not treatable with IT therapy, etc.)
4. Psychological or other health conditions, financial and/or legal concerns that would interfere with the subject's ability to fulfill the requirements of the protocol as per the investigator's discretion

5. Substance Use Disorder (SUD) within the last 2 years or current Medication Assisted Treatment (MAT) for substance use disorder
6. Currently using cannabinoids or illicit drugs
7. History of allergy or significant adverse reaction to morphine per investigator discretion
8. Currently participating or plans to participate in another investigational study unless written approval is provided by Medtronic Study Team

10. Study Procedures

10.1 Summary of Visits

Study procedures and data collection requirements for the study are provided in detail below for each visit and summarized in Table 3: Schedule of Events within Section 10.11. Refer to Section 6, Figure 1: Embrace TDD Study Visit Flowchart for a diagram of the required study visits.

A summary of the required visits are as follows:

- Baseline Visit
- Intrathecal Trial Visit
- Implant Visit
- Post-Op Visit
- 1-Month Visit
- 3-Month Visit
- 6-Month (Study Exit) Visit

Table 2: Visit Windows provides details regarding the study visit windows for all required study visits.

Table 2: Visit Windows

	Study Visits	Visit Windows
IT Therapy Initiation **(Day 0)** Implant to Post-Op Visit	Baseline Visit	Date of Enrollment (Date ICF/HIPAA signed and dated)
	Intrathecal Trial Visit	After Baseline and prior to Implant
	Implant Visit	≤ 150 days after the Baseline Visit
	Post-Op Visit	14 ± 4 days after the Implant Visit
	1-Month Visit	30 days ± 5 days after **Day 0**
	3-Month Visit	90 days ± 10 days after **Day 0**
	6-Month Visit (Study Exit)	180 days ± 10 days after **Day 0**

10.2 Baseline Visit

Subjects are considered enrolled at the time the study-specific informed consent/HIPAA form is signed. At the Baseline Visit, the Medtronic and site Institutional Review Board (IRB) approved informed consent/HIPAA form will be reviewed with the potential subject. If the subject agrees to participate, they will be consented and assessed for eligibility to the study-specific inclusion and exclusion criteria. Each subject must meet all the inclusion criteria and none of the exclusion criteria to be eligible to participate in this study. No study-related procedures or testing will be conducted prior to completing the consenting process of a subject.

Subjects will be asked to complete the VAS for pain intensity and the NOSE assessment tool. Site personnel will confirm the subject's VAS score ≥ 50 mm or the subject's NOSE score ≥ 40 to be eligible to continue in the study. Female subjects of child-bearing potential (not post-menopausal or surgically sterile) must be administered a urine pregnancy test to confirm they are not pregnant at this visit. A subject who has a positive urine pregnancy test will be exited from the study according to Section 10.10. In addition, site personnel must confirm the drug testing results are negative for cannabinoids and illicit drugs for all subjects. If subjects meet all the eligibility criteria, their chronic back (and leg, if applicable) pain history and surgical history will be collected and the study investigator will discuss the process for weaning off systemic opioids with the subject.

Systemic Opioid Weaning and Holiday

Investigators should begin weaning the subject off their systemic opioids on the day of their Baseline Visit (i.e., enrolment date). The method of the opioid weaning process is at the investigator's discretion, but must be completed within the following constraints:

- Total duration (Baseline to Implant ≤ 5 months)
- Systemic opioid dose of ≤ 60 MME before IT trial
- Minimum opioid holiday of at least 7 days prior to IT Therapy Initiation

If a subject has been enrolled in the study and is determined to be ineligible during the Baseline Visit, or they choose to withdraw early, the subject will be exited according to Section 10.10.

Data Collection Requirements for the Baseline Visit:

- ICF/HIPAA
- Inclusion/exclusion criteria
- VAS
- NOSE
- Demographics
- Back (and leg, if present) pain history/surgical history
- Adjunctive pain management therapies utilized
- Urine pregnancy test results, if applicable
- Drug testing for systemic opioids, cannabinoids, and illicit drug use
- Pain medications
- AEs

10.3 Intrathecal Trial Visit

Site personnel must ensure the subject meets eligibility criteria prior to initiating any IT drug trial procedures. Subjects will be asked to complete the VAS for pain intensity and the NOSE assessment tool. The investigator must then confirm the subject's systemic opioid dose is ≤ 60 MME prior to moving forward with the IT drug trial. Females of child-bearing potential (not post-menopausal or surgically sterile) must be administered a urine pregnancy test at this visit to confirm they are not pregnant. In addition, site personnel must confirm each subject's drug testing results for systemic opioids and confirm results are negative for cannabinoids and illicit drugs. If it is determined the subject no longer meets eligibility criteria, or they choose to withdraw early, the subject will be exited from the study according to Section 10.10.

The IT trial will be conducted according to the investigator's standard of care procedures. A successful IT trial will be determined by the investigator and documented accordingly.

If the investigator determines the IT trial was not successful, the subject will be considered a screen failure and will be exited from the study according to Section 10.10.

Data Collection Requirements for the IT Trial Visit:

- Inclusion/exclusion criteria
- VAS
- NOSE
- Adjunctive pain management therapies utilized
- Urine pregnancy test results, if applicable
- Drug testing results for systemic opioids, cannabinoids, and illicit drugs
- Date systemic opioids were stopped, if prior to trial
- IT trial method, drug name, lot number/identifier, dose(s) and concentration(s)
- Pain medications
- AEs

10.4 Implant Visit

The Implant Visit must occur ≤150 days after the Baseline Visit. Females of child-bearing potential (not post-menopausal or surgically sterile) must be administered a urine pregnancy test within 2 weeks prior to the implant visit to confirm they are not pregnant.

Only investigators who are trained and experienced in implanting the SynchroMed II infusion system and trained by Medtronic on the study requirements will be qualified to perform the implant. The IDDS will be implanted per the investigator's standard procedures. Investigators performing the implant should obtain a final intra-operative fluoroscopy or anteroposterior and lateral x-ray to confirm catheter placement. Initial device interrogations and data uploads must be completed at implant and final interrogation prior to discharge.

The investigator may determine whether to initiate IT therapy at the Implant Visit or after the Implant Visit and up to the date of the Post-Op Visit. If IT therapy is initiated at the Implant, refer to Section 10.6 for IT Therapy Initiation requirements. PFMS dosing will be managed according to the IT PFMS administration and dosing parameters outlined in Section 10.13. If PFMS is not added to the pump at the Implant, then preservative-free sodium chloride can be used to fill the pump until the IT Therapy Initiation occurs.

Non-opioid medications and concomitant therapies may be utilized to manage post-operative pain for up to 14 days post implant. If IT Therapy is not being initiated at the Implant Visit, systemic opioids may be taken to manage post-operative pain but must be discontinued a minimum of 7 days prior to the date of IT Therapy Initiation. Medications prescribed for the treatment of pain will be collected during the study and documented in the subject's medical records and on the applicable Electronic Case Report Form(s) (eCRF).

Use of myPTM for each subject will be at the discretion of the investigator and subject.

Data Collection Requirements for the Implant Visit:

- Date systemic opioids were stopped, if prior to the implant
- Adjunctive pain management therapies utilized
- Confirm urine pregnancy test completed within 2 weeks prior to implant, if applicable
- Final AP and lateral fluoroscopic/x-ray images to confirm catheter tip location
- Device information, (including Model # and Serial/Lot #) will be collected for each of the following:
  - Pump
  - Catheter
  - myPTM (if distributed)
- Initial and final device interrogation reports (at implant and prior to discharge)
- Pain medications
- AEs/DDs

10.5 Post-Op Visit

The Post-Op Visit must occur 14 days ±4 days from the Implant Visit. Investigators should evaluate the subject's implant wound to confirm it has healed appropriately and document any relevant observations in the medical records (source records). The following activities must also be completed during the visit: initial and final device interrogations and data uploads, if device was interrogated, date systemic opioids were stopped (if after implant), pain medications, AEs and DDs must be documented in the subject's source.

Use of myPTM for each subject will be at the discretion of the investigator and subject.

If IT therapy is initiated at this visit, refer to Section 10.6 for IT Therapy Initiation requirements. PFMS dosing will be managed according to the IT PFMS administration and dosing parameters outlined in Section 10.13.

Data Collection Requirements for the Post-Op Visit:

- Date systemic opioids were stopped, if after implant
- Initial and final device interrogation reports
- Pain medications
- AEs/DDs

10.6 IT Therapy Initiation

IT Therapy Initiation may take place any time from the Implant Visit through the Post Op Visit. Subjects will be asked to complete the VAS for pain intensity and the NOSE assessment tool prior to site personnel performing other visit activities. If the IT Therapy Initiation is occurring on a date other than during the Implant Visit, or the Post-Op Visit, females of child-bearing potential (not post-menopausal or

surgically sterile) must be administered a urine pregnancy test at this visit to confirm they are not pregnant, before initiating IT PFMS. In addition, site personnel must confirm the drug testing results are negative for systemic opioids, cannabinoids, and illicit drugs.

Only PFMS and 0.9% solution of preservative-free sodium chloride injection (USP) for dilution will be allowed in the pump from the IT Therapy Initiation Visit through the 6-Month Visit. PFMS dosing will be managed according to the IT PFMS administration and dosing parameters outlined in Section 10.13.

Use of myPTM for each subject will be at the discretion of the investigator and subject. If myPTM will be utilized, the physician may activate myPTM, program the pump accordingly, distribute myPTM to the subject and educate the subject on the use of the myPTM during this visit.

Data Collection Requirements for IT Therapy Initiation:

- VAS
- NOSE
- Date systemic opioids were stopped, if applicable
- Adjunctive pain management therapies utilized
- Urine pregnancy test, if applicable
- Drug testing results for systemic opioids, cannabinoids, and illicit drugs
- Drug information including:
  - Drug name
  - Lot #/identifier
  - Dose
  - Concentration
- Initial and final device interrogation reports
- Pain medications
- AEs/DDs

10.7 1-, 3-, and 6-Month Visits

Visits will be required at 1, 3, and 6 months after IT Therapy Initiation **(Day 0)**. Visit windows are as follow for these visits:

1-Month Visit	30 days ± 5 days after **Day 0**
3-Month Visit	90 days ± 10 days after **Day 0**
6-Month Visit	180 days ± 10 days after **Day 0**

Subjects will be asked to complete the VAS for pain intensity and the NOSE assessment tool prior to site personnel performing other visit activities. VAS and NOSE will be collected at all visits. PFMS dose adjustments may be made during these required follow-up visits or during unscheduled visits if

necessary, to manage subject pain or opioid-related side effects. PFMS dosing will be managed according to the IT PFMS administration and dosing parameters outlined in Section 10.13.

In the event the subject is unable to be managed on morphine monotherapy from the IT Therapy Initiation through the 6-Month Visit, a study deviation eCRF must be completed.

Data Collection Requirements for the 1-, 3-, and 6-Month Visits:

- VAS
- NOSE
- Urine pregnancy test, if applicable
- Drug testing results for systemic opioids, cannabinoids, and illicit drugs
- Actual residual and fill volume (if pump refill occurs during visit)
- Drug information (if pump refill occurs during visit) including:
  - Drug name
  - Lot #/identifier
  - Dose
  - Concentration
- Initial and final device interrogation reports
- Pain medications
- AEs/DDs

[redacted]

10.8 Unscheduled Visits

Unscheduled visits may occur during the study for reasons including dose adjustments, programming adjustments, pump refills, medication changes (if subject is unable to be successfully managed on morphine monotherapy), AEs, and DDs.

Subjects will be asked to complete the VAS for pain intensity and the NOSE assessment tool prior to site personnel performing other visit activities.

PFMS dose adjustments may be made during unscheduled visits if necessary, to manage subject pain or opioid-related side effects. PFMS dosing will be managed according to the IT PFMS administration and dosing parameters outlined in Section 10.13 and pump refills will be handled as required in Section 10.12.

Data Collection Requirements for Unscheduled Visits:

- VAS
- NOSE
- Reason for the unscheduled visit
- Actual residual and fill volume (if pump refill occurs during visit)
- Drug information (if pump refill occurs during visit) including:
  - Drug name
  - Lot #/identifier
  - Dose
  - Concentration
- Initial and final device interrogation reports
- Pain medications
- AEs/DDs

10.9 System Modifications

A system modification must be reported in the event the catheter and/or pump require surgical modification. Programming of a new PFMS dose or refilling the pump are not considered system modifications. In the event of a system modification, the follow-up schedule for the subject will remain unchanged.

Data Collection Requirements for System Modifications:

- VAS
- NOSE
- Reason for system modification and all affected components
- Initial and final device interrogation reports for the existing pump
- Actual residual volume of existing pump
- Drug information (if pump refill occurs during visit) including:
  - Drug name
  - Lot #/identifier
  - Dose
  - Concentration
- Initial and final device interrogation reports for new pump, if applicable
- Pain medications
- AEs/DDs

10.10 Study Exit

Normal study completion occurs when the subject has completed the required study visits through the 6-Month Visit (refer to required procedures described in Section 10.7), at which time the subject will end their participation in the study and site personnel will then complete required eCRFs. If a subject has already completed their 6-Month visit, they will be brought into re-consent, and be exited from the

study. If the subject is an early withdrawal, refer to Section 10.21 for subject withdrawal or discontinuation procedures.

10.11 Schedule of Events

Table 3: Schedule of Events

Study Procedures, Tasks, and Data Collection (row) by Visit (column)	Baseline Visit (Enrollment)	Intrathecal Trial Visit	Implant Visit	Post-Op Visit	IT Therapy Initiation	1-Month Visit	3-Month Visit	6-Month Visit (Study Exit)	Unscheduled Visits
Informed Consent Process	√								
Demographics	√								
Inclusion/Exclusion Criteria	√	√							
Urine Pregnancy Test	√	√	√[1]		√	√	√	√	
Drug Test	√	√			√	√	√	√	
Adjunctive pain management therapies	√	√	√		√				
Back and Leg Pain/Surgical History	√								
VAS	√	√			√	√	√	√	√
NOSE Assessment	√	√			√	√	√	√	√
IT PFMS Dose					√	√	√	√	√
[redacted]									
[redacted]									
[redacted]									
[redacted]									
[redacted]									
[redacted]									
Fluoroscopy/x-ray			√						
Device information (model, serial/lot #)			√						
Drug information (name, lot #/identifier, dose & concentration)		√			√	√	√	√	√
Initial and final device interrogation reports			√	√	√	√	√	√	√
Collect AEs/DDs	√[2]	√	√[2]	√	√	√	√	√	√
Pain Medications	√	√	√	√	√	√	√	√	√

[1]Confirm pregnancy test completed within 2 weeks prior to implant visit

[2]Device Deficiencies will be collected and reported from the Implant Visit through the 6-Month Visit/Study Exit

10.12 Pump Refills

Pump refills will be performed by study investigators or appropriately delegated personnel experienced with the use, filling, and dose modification of SynchroMed II infusion system.

- Pump refill procedures may occur at scheduled or unscheduled visits.
- Careful monitoring of the refill schedule must be done to prevent reservoir depletion and potential adverse events.
- Any drug remaining in the pump reservoir at the time of refill should be removed and discarded, and the pump reservoir should be refilled (document the actual residual volume, the refill volume, the drug concentration, and dose in the subject's medical record).

Refer to Section 10.13, for managing IT PFMS dose increases and decreases, including information on dosing limits. Refer to the SynchroMed II Programmable Pumps Implant Manual for the complete instructions pertaining to pump refill procedures.

10.13 IT PFMS Administration and Dosing

Intrathecal study drug will be administered using commercially available Medtronic SynchroMed II infusion systems. IT PFMS initiation and subsequent dosing adjustments are determined based on specific patient needs and clinician standard practices but must be within the following evidence-based consensus guidelines and remain in line with study dosing goals.

IT PFMS Dosing Goal:

To maintain or improve pain control and/or opioid-related side effects (compared to Baseline) with utilization of the lowest reasonable daily dose of IT PFMS following discontinuation of all systemic opioids and implant of the SynchroMed II infusion system.

PFMS, at a concentration not exceeding 25 mg/mL and 0.9% solution of preservative-free sodium chloride injection (USP) for dilution, will be the only drug allowed in the pump from the IT Therapy Initiation Visit through the duration of the study, if possible.

IT PFMS Dose Initiation Parameters:

IT PFMS may be initiated at Implant, the Post-Op Visit, or any time in between per investigator standard practice and patient-specific therapy needs. Standard guidelines for intrathecal PFMS dosing initiation include:

- A starting PFMS dose of 0.1 to 0.5 mg/day, or half the effective trial dose, with lower initial PFMS doses considered, as needed, dependent upon the duration of opioid holiday. Determination of IT PFMS dosing based on previous systemic opioid dosing is not recommended.
- A starting concentration to achieve an estimated pump refill interval of 120 days, but not to exceed 180 days

- Patients may initiate myPTM use at any point during the study.

IT PFMS Dose Adjustment Parameters:

Study investigators or appropriately trained and delegated designees experienced with the use, filling, and dose modification of the SynchroMed II infusion system will be responsible for administering and adjusting PFMS doses in this study. The investigator is responsible for overseeing and managing dosing in accordance with the IT dosing goal and the following instructions:

- IT PFMS dose increases or decreases can be made any time throughout the duration of study.
- IT PFMS Dose adjustments (increase or decrease) completed outside of a protocol-required visit will be considered an Unscheduled Visit. Initial PFMS dose increases following implant may be higher depending on the starting IT PFMS dose. Subsequent increases should only be made in response to inadequate pain control with increases as low as possible, but not exceeding 25%, to achieve adequate pain control

10.14 Prior and Concomitant Medications

Only those subjects who are on a daily dose of > 0 and ≤120 MME of systemic opioids (at the time of enrollment) will be eligible for participation in the study. Medications prescribed for the treatment of pain will be collected during the study and documented in the subject's medical records and on the applicable eCRF(s). Non-opioid medications and concomitant therapies may be utilized throughout the study and to manage post-operative pain at the discretion of the investigator, although it is recommended that these medications remain as stable as possible or be decreased as appropriate. Increases in these medications are discouraged. Systemic opioids may be taken to manage post-operative pain, if IT therapy is not being initiated at the Implant Visit, as long as the subject has a minimum of a 7-day opioid holiday prior to the date of IT Therapy Initiation.

10.15 Subject Consent

Investigators shall consider for enrollment all subjects who meet eligibility requirements for study participation to avoid any bias in the subject population. Prior to enrolling subjects, each investigational site's IRB will be required to approve the CIP, ICF and HIPAA/data protection authorization or other privacy language (where required by law), and any other written study information to be provided to the subjects (e.g. CA Bill of Rights if applicable, subject assessments). The document(s) must be controlled (i.e. version number and date) to ensure it is clear which version(s) were approved by the IRB. Any adaptation of the informed consent form must be reviewed and approved by Medtronic as well as the IRB prior to enrolling subjects. The ICF will be provided separately.

Patient informed consent is defined as legally effective, documented confirmation of a subject's voluntary agreement to participate in a clinical study after information has been given to the subject on all aspects of the clinical study that are relevant to the subject's decision to participate. The informed

consent process will be performed and documented by the study team in accordance with the ethical principles that have their origin in the Declaration of Helsinki and in accordance with 21 CRF Part 50.

Prior to entering the study, the PI, or appropriately delegated designee, will explain to each subject all aspects of the clinical investigation that are relevant to the subject's decision to participate throughout the clinical investigation including, but not limited to, the following: purpose and nature of the study, study procedures, expected study duration, available alternative therapies, and the benefits and risks involved with study participation and the potential treatment.

The investigator shall seek such consent only under circumstances that provide the prospective subject sufficient opportunity to consider whether to participate, and that minimize the possibility of coercion or undue influence. No informed consent, whether oral or written, may include any exculpatory language through which the subject is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution, or its agents from liability for negligence.

Subjects are considered enrolled at the time the study-specific ICF is signed. Informed consent must be obtained from the subject prior to initiation of any study-specific procedures. Subjects must be able to personally sign and date the consent form to participate in this study. Signing and dating of the ICF or HIPAA authorization form by a legally authorized representative will not be permitted for this study. Subjects will be required to sign and date a HIPAA authorization form before participating sites can collect, use and submit subject information to the study sponsor. The Consent Form and Authorization to Use and Disclose Personal Health Information/ Research Authorization/other privacy language, as required by law, must be given to the subject in a language he/she is able to read and understand.

As the ICF is expected to be signed on the same day, but prior to any Baseline Visit study-related procedures, it will be documented in the subject's case history and consent documentation that consent was obtained prior to participation in any study related procedures.

The signed and dated ICF must be filed in the hospital/clinical chart and/or with the subject's study documents. A copy of the informed consent form and signed Authorization to Use and Disclose Personal Health Information/Research Authorization/other privacy language, as required by law, must also be provided to the subject.

The signed and dated informed consent form and Authorization to Use and Disclose Personal Health Information/Research Authorization/other privacy language, as required by law, as well as documentation of the individual informed consent process must be available for monitoring and auditing.

Any changes to a previously approved informed consent form throughout the course of the study must be submitted to and approved by Medtronic and the IRB reviewing the application before being used to

consent a prospective study subject. The document(s) must be controlled (i.e. versioned and dated) to ensure it is clear which version(s) are approved and current by the IRB.

The investigator must notify the subject of any significant new findings about the study that become available during the study which are pertinent to the safety and well-being of the subject, as this could impact a subject's willingness to continue participation in the study.

10.16 Medication Compliance

Subjects will be required to wean off all systemic opioids prior to IT Therapy Initiation. Drug testing (urine, blood, or oral fluid) will be administered at the Baseline Visit to confirm the subject is not currently taking any cannabinoids or illicit drugs. Patients will be weaned off all systemic opioids and adhere to a strict opioid-free holiday period of at least 7 days prior to initiating IT PFMS therapy. Confirmation that the patient has successfully ceased taking systemic opioids and is not taking any cannabinoids or illicit drugs will be confirmed via drug testing prior to the initiation of IT PFMS therapy. Drug testing will be completed at each scheduled follow-up visit after the initiation of IT morphine monotherapy through the 6-Month/Study Exit Visit to confirm they are compliant and not taking any systemic opioids, cannabinoids, or illicit drugs.

10.17 Assessment of Efficacy

10.17.1 Visual Analog Scale (VAS)

Pain will be assessed using VAS. The VAS is a 100 mm line, with "No pain" on the left side of the line and "Worst pain imaginable" on the right side of the line. Subjects will be asked to mark a line perpendicular to the VAS line that best describes their average pain in the last 24 hours.

10.17.2 Numerical Opioid Side Effect Assessment Tool (NOSE)

The Numerical Opioid Side Effect (NOSE) Assessment Tool is a tool to evaluate 10 opioid-related side effects using a 11-point numeric scale.[19] Subjects are asked to evaluate each of the 10 opioid-related side effects on a scale of 0-10 with 0 being not present and 10 being as bad as you can imagine. A total sum score can range from 0-100. The opioid side effects included: 1) Nausea, vomiting, and/or lack of appetite; 2) Fatigue, sleepiness, trouble concentrating, hallucinations, and/or drowsiness/somnolence; 3) Constipation; 4) Itching; 5) Decreased sexual desire/function and/or diminished libido; 6) Dry mouth; 7) Abdominal pain or discomfort/cramping or bloating; 8) Sweating; 9) Headache and/or dizziness; 10) Urinary retention. The score from each side effect as well as the total sum score from all side effects may be reported.

[redacted]

[redacted]

10.18 Assessment of Safety

Subjects will be assessed from enrollment through the end of the study for AEs related to the following:

- Systemic opioid weaning

- Device
- IT drug
- Procedure

In addition, all SAEs (regardless of relatedness) and device deficiencies reported during the study will be collected. All subject deaths (regardless of relatedness) must be reported to Medtronic according to Section 12.6.

10.19 Recording Data

This study will be utilizing a Remote Data Capture (RDC) system to collect study required Case Report Form (CRF) information. Electronic CRFs (eCRFs) will be provided by the sponsor; required data will be recorded from source documents and entered into the study database via the eCRFs by the appropriately delegated site personnel, in accordance with applicable regulations. Source documentation for VAS and other subject assessments will be captured in a paper format and completed confidentially by the subject only. Source documentation for NOSE will be captured in a paper format and completed by the PI or delegated sub-investigator. Data from the paper assessments will be entered into the database by delegated site personnel after ensuring the completeness and accuracy of the data.

The PI or appropriately delegated individuals are responsible for entering data for the study on the eCRFs. The PI or delegated sub-investigator (physician only) is required to approve all data on eCRFs via electronic signature.

SynchroMed II programming data (interrogation and pump programming parameters) captured and recorded by the Clinician Programmer Model A810 application will be uploaded to a secure database. The Clinical Data Upload application is a tool available for installation on and use with the Clinician Programmer that allows clinicians to electronically transfer and save session data files to a secure Medtronic database.

10.20 Deviation Handling

A deviation is defined as an instance(s) of failure to follow, intentionally or unintentionally, the requirements of the clinical investigational plan. The investigator is not allowed to deviate from the CIP, except under emergency circumstances to protect the rights, safety and well-being of human subjects.

All study deviations must be reported on the eCRFs regardless of whether medically justifiable, pre-approved by Medtronic, an inadvertent occurrence, or taken to protect the subject in an emergency.

Study deviations must be reported to Medtronic as soon as possible upon the site becoming aware of the deviation. Reporting of deviations must comply with IRB policies, local laws, and/or regulatory agency requirements.

If a deviation involves a failure to obtain a subject's consent or the deviation is made to protect the life or physical well-being of a subject in an emergency, the deviation must be reported to the IRB as well as Medtronic within five (5) working days.

In situations where the investigator anticipates, contemplates, or makes a conscious decision to deviate from the CIP, the investigator must provide Medtronic with his/her request to deviate from the CIP. Medtronic will respond to all requests in writing. If approved, and the deviation affects a subject's rights, safety and well-being, or the scientific integrity of the study, prior approval from IRB is also required.

Prior written approval from Medtronic is not required when a deviation is necessary to protect the rights, safety or well-being of a subject in an emergency or in unforeseen situations beyond the investigator's control (e.g. subject failure to attend scheduled follow-up visits, inadvertent loss of data due to computer malfunction, inability to perform required procedures due to subject illness).

Medtronic is responsible for analyzing deviations, assessing their significance, and identifying any additional corrective and/or preventive actions (e.g. amend the CIP, conduct additional training, or terminate the investigation). Repetitive or serious investigator compliance issues may result in initiation of a corrective action plan with the investigator and site, and in some cases, necessitate suspending enrollment until the problem is resolved or ultimately terminating the investigator's participation in the study.

Examples of study deviations include but are not limited to the following:

- Failure to obtain informed consent or HIPAA authorization prior to study enrollment
- Failure to re-consent when new information is added and approved
- Use of an outdated consent
- Unqualified or non-delegated personnel perform consent process
- Violation of inclusion/exclusion criteria
- Failure to collect protocol required assessments procedures (e.g., VAS data, subject assessment missing)
- Missed visits
- Visits outside of window
- Missing source documentation
- Use of expired device or unapproved device
- Use of drug(s) not allowed per the protocol (i.e. systemic opioids after initiation of IT therapy, cannabinoids, illicit drugs)
- Addition of infusion drugs other that PFMS
- Unauthorized personnel performing study procedures

10.21 Subject Withdrawal or Discontinuation

A subject has the right to withdraw from the study at any time and for any reason without prejudice to his/her future medical care by the PI or institution. Subjects will be provided standard medical care by their physician after their study participation ends.

The study sample size accounts for potential attrition. Therefore, subjects that discontinue after enrollment in the study will not be replaced.

If a subject is withdrawn from the study, the reason for withdrawal shall be recorded on a study exit eCRF and in the subject's medical record.

Examples of reasons for study discontinuation include, but are not limited to, the following:

- Eligibility criteria not met (prior to implant)
- Pregnancy
- Subject death
- Subject lost to follow-up (LTFU)
- Subject voluntarily withdraws from the study
- Adverse events
- Normal study completion

A study exit eCRF must be completed for any enrolled subject who permanently discontinues from the study regardless of whether they discontinue early or complete the protocol-required study follow-up and has completed the study.

Study site personnel must make a minimum of three attempts to contact a subject before a subject can be considered LTFU for this study. Site personnel must document those attempts and the method of attempt (e.g. two by phone and one by certified letter) to contact the subject in the subject's medical and/or study records. In addition, any other requirements set forth by the governing IRB must be followed.

The investigator should make all attempts to conduct an in-office discontinuation visit prior to subject withdrawal if the subject is withdrawn after the device is implanted. All eCRFs should be completed for visits that occurred prior to the subject's withdrawal. In addition, regardless of when the discontinuation occurs, site personnel should request an update on the status of any medications, ongoing adverse event or device deficiency. If a subject discontinues prior to completing the 6-Month Visit, site personnel should request the subject complete all applicable subject assessments required at the 6-Month Visit, if the subject is willing, to ensure final assessments for the study are obtained whenever possible.

11. Risks and Benefits

11.1 Potential Risks

The SynchroMed II infusion system, which includes a SynchroMed II implantable pump, implantable catheters, accessory kits, and clinician and patient therapy applications, is commercially available in the United States. The risks associated with the products and procedures are no different than those for SynchroMed II infusion system patients outside of this clinical study. Risks are disclosed in the device labeling included with each product. Refer to the appropriate device labeling for all current risks, contraindications, warnings and precautions. Risks associated with the use of PFMS are no different for subjects participating in this study than they are for patients who receive PFMS outside of this clinical study. Risks are disclosed in the drug labeling included with the product. Refer to the appropriate drug labeling for all current risks, contraindications, warnings, precautions, dosage and administration information and screening procedures. As such there is no incremental risk associated with the participation in the Embrace TDD Clinical Study.

Systemic Opioid Weaning Risks:

Investigators must review risks associated with systemic opioid weaning with each study subject. Opioid withdrawal symptoms may vary depending on each's subjects current regimen of systemic opioids, and the method(s) utilized to assist with the weaning may impact any associated risks. Examples of withdrawal symptoms may include, but are not limited to the following:

- Headache
- Muscle aches, restlessness
- Anxiety
- Insomnia
- Diarrhea
- Nausea and vomiting
- Rapid heartbeat

Risks associated with Implantation or Use of an infusion system:

- Pocket seroma, hematoma, erosion, or infection
- Infection
- Pump inversion ("flipping")
- Placement of the catheter may expose patients to risks of postlumbar puncture (spinal headache), cerebral spinal fluid (CSF) leak and CSF subcutaneous collection or rare central nervous system (CNS) pressure-related problems, radiculitis, arachnoiditis, bleeding, spinal cord damage, or meningitis
- Inflammatory mass could result in neurological impairment, including paralysis

- Allergic or immune system response to the implanted materials. A listing of device materials can be found in the Device Specifications sections of the implant manuals for the pump and catheters

System- and Procedure-Related Complications:

Possible system complications listed below can result in overdose symptoms, tissue damage, or a loss of or change in therapy, which might lead to a return of underlying symptoms, drug withdrawal symptoms, serious injury, or death and might require surgery to replace or remove the pump, catheter, or catheter fragment. These complications include:

- End of device service life or component failure, requiring surgical replacement
- Component failure, resulting in loss of therapy, drug overdose, or inability to program the pump
- The pump, catheter, or catheter fragment could migrate within the body or erode through the skin
- The implanted materials could cause an allergic or immune system response
- There could be undesirable changes in therapy, possibly related to cellular changes around the tip of the catheter
- An inflammatory mass that could result in serious neurological impairment, including paralysis
- The catheter could leak, tear, or become disconnected, resulting in delivery of medication into the area under the skin where the pump is implanted or along the catheter path
- The catheter could kink or become blocked resulting in no delivery of medication
- The pump could stop because it has reached end of service life or because of a component failure
- Catheter damage, dislodgement, migration, disconnection, kinking or occlusion, fibrosis, or hygroma, resulting in tissue damage or a loss of or change in therapy, and contributing to over infusion or other potentially serious adverse health consequences

Risks of implanting an infusion system has risks similar to other surgical procedures, including pain or infection at the implant site after surgery. Implanting an infusion system that will deliver drug to a patient's spine, has risks similar to spinal procedures, including:

- Pump implanted upside down
- Improper handling of components before, during, or after implantation
- Reservoir contamination
- Improper injection through the catheter access port
- Injection into the pocket or subcutaneous tissue
- Activation of the reservoir valve (if present)
- Over pressurization of the reservoir, including by overfilling
- Programming error
- Tunneling during the catheter implant procedure may expose patients to risks of serious injury or death due to perforation of vital organs and/or major blood vessels
- Detached catheter tip or catheter fragment(s) in the intrathecal space

- Residual catheter fragments may migrate, including rarely into the intracranial cavity, potentially resulting in serious adverse health consequences that may require surgical removal
- Residual catheter fragments in the CSF may compromise antibiotic effectiveness in the presence of a concomitant CSF infection

Drug-Related Complications:

- Local or systemic drug toxicity and related side effects
- Symptoms of overdose or underdose
- Inflammatory mass formation at the tip of the implanted catheter particularly in patients who receive intraspinal morphine or other opioid drugs

Refer to the applicable product manual(s) for all current risks, warnings, precautions and contraindications associated with the SynchroMed II infusion system. Product manuals are provided with the products and are also available electronically at:
http://manuals.medtronic.com/manuals/main/region

There may be other risks related to the SynchroMed II infusion system and/or PFMS used in this study that are not foreseen at this time. All anticipated adverse events are the same as those foreseeable risks listed in Section 11.1.

11.2 Pregnancy Risks

Pregnant women are not able to take part in this study. Female subjects must agree to not become pregnant during the study by using a medically acceptable method of birth control. If subjects become pregnant during this study, there may be risks to the subject or their unborn child that are not yet known. Subjects must notify the study doctor immediately if they think they are pregnant or if they become pregnant during the study. Site personnel are responsible for the following:

- Documenting all available information regarding the pregnancy in the source documents and notifying Medtronic study personnel
- Notifying the IRB per the study site's requirements
- Exiting the subject from the study and completing the appropriate eCRF(s) according to Section 10.21

11.3 Risk Minimization (Control Measures)

Each investigator must be familiar with the SynchroMed II infusion system and PFMS. The frequent monitoring of study subjects by an experienced investigator will reduce the risks associated with this study. Each study center will have a staff of physicians and nurses experienced, educated, and trained to care for subjects implanted with a SynchroMed II infusion system. Medtronic will conduct study protocol

training for all study center personnel prior to study initiation. All study personnel will be provided with emergency instructions in the event an underdose or overdose of PFMS causes life-threatening symptoms (Refer to the Technical Manual, "Indications, Drug Stability, and Emergency Procedures for SynchroMed® and IsoMed® Implantable infusion systems" provided separately).

11.4 Potential Benefits

Subjects might not receive any direct medical benefits from participation in this study relative to receiving the therapy outside of the study. By participating in this study, subjects will have access to additional medical oversight or procedures. The information gained from this study may result in improved understanding of this therapy. Subjects may also experience better pain control and fewer side effects. Additionally, information collected from this study may assist in the design of future studies. The study results will be published to increase the body of knowledge about this therapy.

11.5 Risk-Benefit Rationale

Consensus statements and evidence-based systematic reviews have been developed to guide the use of infusion therapy with morphine for chronic intractable pain. Both the SynchroMed II infusion system and PFMS are commercially available, with a positive risk-benefit ratio established for each.

12. Adverse Events and Device Deficiencies

12.1 Definitions / Classifications

Any adverse event (AE) meeting the definition of systemic opioid weaning-related, device-related, IT drug-related, and procedure-related, all serious adverse events and deaths (regardless of relatedness) for all subjects from Baseline to the 6-Month Visit, and device deficiencies (DD) for all subjects from Implant to the 6-Month Visit will be collected. All anticipated AEs and adverse device effects are the same as those foreseeable risks listed in Section 11.1.

This post-market study is not within the scope of ISO 14155:2011 but will use AE definitions according to ISO 14155:2011 for consistency in reporting. Each adverse event is classified according to ISO 14155:2011. Adverse events and device deficiencies are defined below in Table 4 as follows:

Table 4: Adverse Event and Device Deficiency Definitions

Term	Definition
Adverse Event (AE): (ISO 14155:2011 3.2)	Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects,

Term	Definition
	users or other persons, whether or not related to the investigational medical device. *NOTE 1:* This definition includes events related to the investigational medical device or the comparator. *NOTE 2:* This definition includes events related to the procedures involved. *NOTE 3:* For users or other persons, this definition is restricted to events related to investigational medical devices.
Adverse Device Effect (ADE): (ISO 14155:2011 3.1)	Adverse event related to the use of an investigational medical device. *NOTE 1:* This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. *NOTE 2:* This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.
Device Deficiency (DD): (ISO 14155:2011 3.15)	Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. *NOTE*: Device deficiencies include malfunctions, use errors, and inadequate labeling.
Malfunction: (ISO 14155:2011 3.27)	Failure of an investigational medical device to perform in accordance with its intended purpose when used in accordance with the instructions for use or (CIP).
Use Error: (ISO 14155:2011 3.43)	Act or omission of an act that results in a different medical device response than intended by the manufacturer or expected by the user. *NOTE 1:* Use error includes slips, lapses, and mistakes. *NOTE 2:* An unexpected physiological response of the subject does not in itself constitute a use error.
Term	**Seriousness**
Serious Adverse Event (SAE): (ISO 14155:2011 3.37)	Adverse event that a) led to death, b) led to serious deterioration in the health of the subject, that either resulted in 1) a life-threatening illness or injury, or 2) a permanent impairment of a body structure or a body function, or 3) in-patient or prolonged hospitalization, or 4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function, c) led to fetal distress, fetal death or a congenital abnormality or birth defect. *NOTE:* Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event.

Term	Definition
Serious Adverse Device Effect (SADE): (ISO 14155:2011 3.36)	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event
Term	**Relatedness**
Systemic Opioid Weaning-Related	An adverse event related to the systemic opioid weaning process (i.e. opioid-related withdrawal symptoms)
Device-Related	An adverse event that results from the presence or performance (intended or otherwise) of the SynchroMed II infusion system.
IT Drug-Related	Event related to the IT drug delivered by the device. Normally IT drug-related events resolve when the device is turned off or reprogrammed, or the drug is removed from the pump. This category should not include events that resulted from a malfunction of the device (i.e. hardware-related events).
Procedure-Related	An adverse event that occurs due to any procedure related to the IT trial, implant, pump refills, programming, or surgical modification of the system.

12.2 Reporting of Adverse Events

Any AE meeting the definition of systemic opioid weaning-related, device-related (i.e. SynchroMed II infusion system), IT drug-related, and procedure-related (i.e. IT trial, implant or pump refill/reprogramming, system modification), and all serious adverse events and deaths (regardless of relatedness), for all subjects from the Baseline Visit through study exit will be collected.

It is the responsibility of the investigator to identify the occurrence of any reportable adverse events and to ensure all required information is accurately recorded in the subject's medical record and reported to Medtronic on an event eCRF. IRB reporting must be completed in accordance with the policies of the governing IRB. Refer to the eCRF for the information to be reported for each AE.

For AEs that require immediate reporting, initial reporting to Medtronic may be done by phone, fax, or e-mail, or on the eCRF by completing as much information as is available. The AE eCRF must be completed as soon as possible.

In case the investigator requires information from the sponsor in an emergency, the investigator can contact Medtronic using the contact details provided in the synopsis and Section 12.5.

The clinical course of each AE must be followed until the adverse event is resolved, the subject is in a stable condition, or until the subject discontinues from the study. "Ongoing" AEs must be assessed at each study visit. The AE eCRF should be updated when there is a change to the information provided on the form (e.g. change in intervention, outcome, relatedness, etc.).

At the last study visit, the investigator will instruct the subject to provide an update on the status of any ongoing events and report any AE they believe may be related to participation in the study.

12.3 Non-Reportable Events

Examples of events that are not reportable as adverse events for this study include:

- Inability to successfully perform a procedure, unless injury occurs
- A documented pre-existing condition unless there is a worsening of the nature, severity, duration or frequency of that condition if it meets the defined criteria for a reportable adverse event (i.e. systemic opioid weaning, device, IT drug and/or procedure-related)

Table 5 provides a list of common expected surgical AEs. An expected surgical event will not be considered reportable unless it worsens or is present outside the stated timeframe post-procedure.

Table 5: Expected Surgical Adverse Events and Durations

Event Description	Timeframe After Surgical Procedure
Low-grade fever (< 100° or <37.8° C)	48 hours
Anesthesia-related nausea/vomiting	24 hours
Mild to moderate bruising/ecchymosis	7 days
Pocket site / incisional pain	14 days
Seroma	72 hours
Sleep problems (insomnia)	72 hours

12.4 Reporting of Device Deficiencies

Device Deficiency (DD) information will be collected for all subjects from the Implant Visit through the 6-Month Visit and reported to Medtronic on a DD CRF, one for each DD. At the last study visit, the investigator will instruct the subject to provide an update on the status of any ongoing events and report any issue with the device they believe may be related to participation in the study.

12.5 Emergency Contact Details

For emergency contact regarding a SADE/DD, contact the Clinical Study Manager immediately.

24-hour Medtronic contact information for reporting SADEs/DD:

Email: [redacted]

Fax: [redacted]

12.6 Subject Death

The investigator must notify Medtronic immediately and the IRB (as required), after learning of a subject's death (regardless of relatedness). The death should be reported to Medtronic on the event eCRF as soon as possible. The investigator should also attempt to determine, as conclusively as possible, whether such deaths are related to the systemic opioid weaning, device, IT drug, or procedure.

If it is determined that the cause of death was related to systemic opioid weaning, device, IT drug, or procedure:

- A copy of an autopsy report should be provided to Medtronic, if an autopsy is performed
- Medtronic requests that all device system components that were being used at the time of the death be returned to Medtronic for analysis per Section 7.11
- Requested death certificates and/or source documentation if obtained, should be redacted and sent to Medtronic

If the death occurs at a location remote from the study site, it is the study site's responsibility to make three attempts to retrieve all pertinent information related to the subject's death and submit the investigator's death summary of the known events surrounding the death to Medtronic.

13. Data Review Committees

This study will utilize a Clinical Events Committee (CEC) to adjudicate the relatedness and seriousness classifications of all reportable adverse events.

The CEC may request clarification and/or additional information from the PI who reported the event. If the conclusion of the review differs from the PI's assessment, both opinions will be reported back to the investigator and noted in the final study report. Incidence rates will be tabulated using the final CEC determination.

The CEC will be external to Medtronic and independent of the study investigators. The members will have specialties appropriate to the therapeutic area and meet requirements established in the CEC charter.

14. Statistical Design and Methods

14.1 General Aspects of Analysis

Data analysis will be performed by Medtronic-employed statisticians or designees. A validated statistical software package will be used for the analyses of the study results (e.g. SAS version 9.4 or higher).

The Statistical Analysis Plan (SAP) will be developed prior to data analysis and will include a comprehensive description of the statistical methods and reports to be included in the final study report. Any change to the data analysis methods described in the CIP will require an amendment only if it changes a principal feature of the CIP. Any other change to the data analysis methods described in the CIP, and the justification for making the change, will be described in the clinical study report.

14.1.1 Sample Size Justification

Ninety-three subjects have been enrolled into the study with the intent to achieve approximately 67 implanted subjects and at least 50 evaluable subjects at the 6-Month Visit. The sample size of 50 evaluable subjects was chosen to assure acceptable levels of precision for estimation of the primary objective of Clinical Success and provide adequate power to test the secondary objective related to pain score.

There were no available data in the target population on the primary objective of Clinical Success, nor on the secondary objective of opioid-related side effects score. The secondary objective of pain intensity score is used for sample size calculation. It is hypothesized that the pain intensity score of VAS at the 6-Month Visit is non-inferior to those at Baseline using a non-inferiority approach.

The PASS 11 Non-Inferiority Tests for One Mean was used to calculate the power for pain intensity of VAS with the following assumptions: Sample size = 50, Alpha = 0.025, Non-Inferiority Margin = 1, True Difference = 0, Standard Deviation = 1.9, with Higher Means are Better (one-sided) t-test. A sample size of 50 would achieve 95% power with the above assumptions. This power calculation was performed using a pain scale of 0-10; however, the power calculation is identical to one with a non-inferiority margin of 10 and assuming a standard deviation of 19 on a VAS pain scale of 0-100.

The non-inferiority margin of 10 points (for the VAS of 0-100) was chosen based on a review of pain study literature. Non-inferiority margins between 1 and 1.5 were reported for pain scales of 0-10, including one study in a similar population of chronic non-malignant pain subjects comparing 2 oral opioids that utilized a margin of 1[d]. The non-inferiority margin of 1 on a pain scale of 0-10 is equivalent to a non-inferiority margin of 10 on a VAS pain scale of 0-100. The estimated actual difference was assumed to be 0 because the goal is to achieve same or better pain control as compared to Baseline.

[redacted]

A 33% attrition between enrollment and subject implant is assumed and a 25% attrition between Implant and the 6-Month Visit is assumed. Under CIP V2.0, approximately 100 subjects were to be enrolled; 93 subjects have been enrolled into the study with the intent to achieve approximately 67 implanted subjects and 50 evaluable subjects at the 6-Month Visit.

[d] Binsfeld H, Szczepanski L, Waechter S, Richarz U, Sabatowski R. A randomized study to demonstrate noninferiority of once-daily OROS® hydromorphone with twice-daily sustained-release oxycodone for moderate to severe chronic noncancer pain, *Pain Pract.* 2010;10(5):404–415.

The 33% attrition between enrollment and subject implant accounts for the subjects who don't meet inclusion and/or exclusion criteria, those who can't follow the weaning process to eliminate systemic opioids, those who don't have a successful IT trial, those who have AE that can no longer be followed in the study, withdrawals, and lost-to-follow-up, etc. The attrition between implant and the 6-Month Visit is conservatively set at 25% to potentially account for the subjects who have adverse events that can no longer be followed in the study, withdrawals, are LTFU, or subjects who can't be effectively managed on morphine monotherapy.

14.1.2 Investigation Site Pooling

The investigators of this study will conduct the study according to this protocol and use the same CRFs to collect study data. The site study personnel will be trained prior to the study initiation at each site. Periodic study monitoring by Medtronic will ensure compliance with protocol requirements.

There is no a priori provision to exclude any sites from the analysis. The data from all sites will be pooled for analysis. To reduce the possibility of atypical results from a site overly influencing the combined results, no more than 15 subjects will be enrolled at each site unless the site gets pre-approval from the Medtronic for additional enrollments.

14.1.3 Other Specific Considerations

Adjustment for Baseline Covariates

There is no plan to make adjustment for Baseline covariates for the primary objective.

Handling Missing Data

Missing data are a potential source of bias when analyzing study data. A rigorous study design and execution will help prevent the incidence of missing data from occurring.

The primary analysis of the primary and secondary objectives will include subjects who maintain morphine monotherapy and provide data (per-protocol population). Sensitivity analyses will be performed for the primary and secondary objectives using the Multiple Imputation (MI) methodology for missing data in VAS and NOSE scores for all implanted subjects. Details of the imputation method are described in Sections 14.4.1 and 14.4.2.

Adjustment for Multiple Endpoints

As there is no hypothesis testing for the primary objective, adjustment for multiple endpoints is not required.

Interim Analysis

There is no planned interim analysis for the primary and secondary objectives in this study.

14.1.4 Reports

A final clinical study report will be generated for this study. Periodic progress reports may also be generated for the study.

14.2 Demographics

Demographics and Baseline characteristics will be summarized in the report for enrolled subjects, implanted subjects, and per-protocol subjects for the primary objective.

14.3 Primary Objective – Clinical Success at the 6-Month Visit

To characterize the proportion of subjects with Clinical Success at the 6-Month Visit based on changes in pain intensity using the Visual Analog Scale (VAS) and changes in opioid-related side effects using the Numerical Opioid Side Effect (NOSE) Assessment Tool.

Hypothesis

There is no formal hypothesis. The objective is to estimate the proportion of Clinical Success at the 6-Month Visit.

Experimental Design

The Clinical Success is comprised of 2 separate measures, pain intensity and opioid-related side effects. The measurements of pain intensity using VAS and opioid-related side effects using NOSE are described in Sections 10.17.1 and 10.17.2. Both pain intensity and opioid-related side effects are measured as a percent change from Baseline to the 6-Month Visit to calculate the Clinical Success.

Pain Intensity:

Percent change in pain intensity will be calculated as VAS at the 6-Month Visit minus VAS at Baseline, then divided by VAS at Baseline, expressed as a percentage. Individual subject percent change in pain intensity is categorized into three responder groups at the 6-Month Visit:

- Worse than Baseline: percent of change in VAS ≥ 20% (increased equal or more than 20%) if Baseline VAS is ≥10 or change in VAS is ≥ 2 if Baseline VAS is < 10
- Equal to Baseline: percent of change in VAS < 20% and > -20% (increased less than 20% or decreased less than 20%) if Baseline VAS is ≥10 or change in VAS is between -2 and 2 if Baseline VAS is < 10
- Better than Baseline: percent of change in VAS ≤ -20% (decreased equal or more than 20%) if Baseline VAS is ≥10 or change in VAS is ≤ -2 if Baseline VAS is < 10

Opioid-Related Side Effects:

Percent change in NOSE will be calculated as NOSE at the 6-Month Visit minus NOSE at Baseline, then divided by NOSE at Baseline, expressed as a percentage. Individual subject percent change in NOSE is categorized into three responder groups at the 6-Month Visit:

- Worse than Baseline: percent of change in NOSE ≥ 20% (increased equal or more than 20%) if Baseline NOSE is ≥10 or change in NOSE is ≥ 2 if Baseline NOSE is < 10
- Equal to Baseline: percent of change in NOSE < 20% and > -20% (increased less than 20% or decreased less than 20%) if Baseline NOSE is ≥10 or change in NOSE is between -2 and 2 if Baseline NOSE is < 10
- Better than Baseline: percent of change in NOSE ≤ -20% (decreased equal or more than 20%) if Baseline NOSE is ≥10 or change in NOSE is ≤ -2 if Baseline NOSE is < 10

Clinical Success:

A subject's Clinical Success is defined as any of the following and displayed in Figure 2:

1. Reduced opioid-related side effects with equal pain
2. Reduced pain with equal opioid-related side effects
3. Reduced pain and reduced opioid-related side effects

Figure 1: Clinical Success

Change from Baseline to the 6-Month Visit			Opioid-Related Side Effects (NOSE)		
			≥20% Increase	< ±20% Change	≥20% Reduction
			Worse	Equal	Better
Pain Intensity (VAS)	≥20% Increase	Worse			
	< ±20% Change	Equal			1
	≥20% Reduction	Better		2	3

Analysis Methods

The proportion of subjects with Clinical Success and its exact binomial two-sided 95% confidence interval will be reported. The primary analysis method will use all the implanted subjects who maintain

morphine monotherapy and provide data at both Baseline and the 6-Month Visits (per-protocol population). Assuming the estimated proportion of Clinical Success is 70%, with a sample size of 50 subjects, the exact two-sided 95% confidence interval (CI) would be 55.4-82.1%, with a confidence width of 26.7%. The widest 95% CI would be at 28.9% for an estimated proportion of Clinical Success of 50% (95% CI 35.5-64.5%).

Two sensitivity analyses will be performed: the proportion of subjects with Clinical Success and its 95% CI will be reported in subjects who provide data at the 6 Month Visit (completers) as well as in all implanted subjects with imputation method of MI for those who has missing VAS or NOSE at the 6-Month Visit. Details of the imputation method are described in Sections 14.4.1 and 14.4.2.

14.4 Secondary Objectives

There are three secondary objectives in the study.

14.4.1 Secondary Objective #1 – VAS Pain Intensity at the 6-Month Visit

To demonstrate pain intensity scores (VAS) at the 6-Month Visit is non-inferior to VAS at Baseline.

Hypothesis

The mean change in pain intensity using VAS from Baseline to the 6-Month Visit is not worse than 0 by more than 10 points.

H_0: $\mu \geq 0 + |M|$

H_A: $\mu < 0 + |M|$

Where μ is the mean change in VAS from Baseline to the 6-Month Visit and $|M|$ is the absolute value of non-inferiority margin of 10.

Experimental Design

The measurements of pain intensity using VAS is described in Section 10.17.1. The change in VAS is calculated using VAS at the 6-Month Visit minus VAS at the Baseline Visit. A negative change is an improvement.

Analysis Methods

The change in VAS as well as VAS at both Baseline and the 6-Month Visit will be summarized using descriptive statistics, (e.g., mean, standard deviations, etc.). The non-inferiority null hypothesis will be tested using a one-sided 0.025 alpha level one sample t-test. The upper bound of the 95% CI of the mean change must be less than 10. If non-inferiority is met, a two-sided 0.05 alpha level t-test for superiority (vs. 0 change from Baseline) will be performed. If the distribution of the change in VAS doesn't meet normality assumption, an appropriate non-parametric analysis will be performed. The

primary analysis will use all the implanted subjects who maintain morphine monotherapy and provide data at both Baseline and 6-Month Visits.

Two sensitivity analyses will be performed, one will include subjects who provide data (completers) and one will include all implanted subjects. The sensitivity analysis of all implanted subjects will be performed using MI method for missing data at the 6-Month Visit. For scheduled 6-Month Visit, if an Unscheduled Visit occurred within the 6-Month Visit window, and the VAS is collected at the Unscheduled Visit, the VAS from the Unscheduled Visit will be used in the analysis of the 6-Month Visit. Otherwise, the missing VAS will be imputed using MI. Prior to the use of MI, the distributions of the continuous variables will be assessed for normality and the need for transformation if they are not normally distributed. The model variables in MI may include study site, subject age, gender, primary diagnosis, VAS at Baseline, 1-Month Visit, 3-Month Visit. The fully conditional specification method with 10 burn-in iterations within SAS and 10 repetitions (M = 10) will be used for imputation. Constraints will be set so that the imputed VAS are restricted to values ranging from 0-100. Following imputation, the objective will be evaluated using MI analysis method.

In addition, percentage of change in VAS will be calculated using change in VAS divided by VAS at Baseline. A negative percentage of change in VAS is a percentage of reduction in VAS, thus an improvement. The percentage of change in VAS will be summarized using descriptive statistics, (e.g., median and inter-quartile range)

14.4.2 Secondary Objective #2 – NOSE Score

To characterize the change in opioid-related side effects scores (NOSE) from Baseline to the 6-Month Visit.

Hypothesis

There is no formal hypothesis. The objective is to estimate the change in NOSE from Baseline to the 6-Month Visit.

Experimental Design

The measurements of opioid-related side effects NOSE are described in Section 10.17.2. The change in NOSE is calculated using NOSE at the 6-Month Visit minus NOSE at Baseline. A negative change is an improvement.

Analysis Methods

The change in NOSE will be summarized using descriptive statistics, (e.g., mean, standard deviations, etc.). The analysis will use all the implanted subjects who maintain morphine monotherapy and provide data at both Baseline and the 6-Month Visits.

Two sensitivity analyses will be performed, one will include subjects who provide data (completers) and one will include all implanted subjects. The sensitivity analysis of all implanted subjects will be

performed using MI method for missing data at the 6-Month Visit. For scheduled 6-Month Visit, if an Unscheduled Visit occurred within the 6-Month Visit window, and NOSE is collected at the Unscheduled Visit, the NOSE from the Unscheduled Visit will be used in the analysis of the 6-Month Visit. Otherwise, the missing NOSE will be imputed using MI. Prior to the use of MI, the distributions of the continuous variables will be assessed for normality and the need for transformation if they are not normally distributed. The model variables in MI may include study site, subject age, gender, primary diagnosis, NOSE at Baseline, 1-Month Visit, 3-Month Visit. The fully conditional specification method with 10 burn-in iterations within SAS and 10 repetitions (M = 10) will be used for imputation. Constraints will be set so that the imputed NOSE are restricted to values ranging from 0-100. Following imputation, the objective will be evaluated using MI analysis method.

In addition, percentage of change in NOSE will be calculated using change in NOSE divided by NOSE at Baseline. A negative percentage of change in NOSE is a percentage of reduction in NOSE, thus an improvement. The percentage of change in NOSE will be summarized using descriptive statistics, (e.g., median and inter-quartile range, etc.).

14.4.3 Secondary Objective #3 – Systemic Opioids Elimination

To characterize the proportion of subjects who eliminate systemic opioids through the 6-Month Visit.

Hypothesis

There is no formal hypothesis. The objective is to estimate the proportion of subjects who eliminate systemic opioids through the 6-Month Visit.

Experimental Design

The test for systemic opioids, cannabinoids, and illicit drug use will be collected at all scheduled study visits except the Implant Visit. If a subject has a negative test for systemic opioid use, this subject will be considered as having eliminated systemic opioids at the scheduled study visit.

Analysis Methods

The proportion of subjects who eliminate systemic opioids and its exact binomial two-sided 95% CI will be reported at the 6-Month Visit as well as for those having eliminated systemic opioids from therapy initiation through the 6-Month Visit. The primary analysis method will use all the implanted subjects who maintain morphine monotherapy and provide data at the 6-Month Visit. Assume the estimated proportion is 80%, with a sample size of 50 subjects, the exact two-sided 95% CI would be 66.3-90.0%, with a confidence width of 23.7%. The widest 95% CI would be at 28.9% for an estimated proportion of 50% (95% CI 35.5-64.5%).

Two sensitivity analyses will be performed, one will include subjects who provide data (completers) and one will include all implanted subjects. The sensitivity analysis in all implanted subjects' analysis will display the full range on the potential impact of missing data by running an analysis assuming all missing

values had eliminated systemic opioids to none of the missing values having eliminated systemic opioids.

14.6 Safety Assessment

To characterize all systemic opioid weaning-related, device-related, IT drug-related, and procedure-related adverse events (AEs), all serious adverse events (SAEs) (regardless of relatedness), and device deficiencies (DD) for all subjects from enrollment until the subject exits.

15. Ethics

15.1 Statement(s) of Compliance

This study will be conducted in compliance with this CIP and Good Clinical Practices according to the United States (US) Code of Federal Regulations (CFR) on Electronic records (21 CFR§11), Protection of Human Subjects (21 CFR§50), Institutional Review Boards (21 CFR §56), Medical Device Reporting (21CFR§803), International Conference on Harmonization (ICH GCP E6) the ethical principles that

originate from the Declaration of Helsinki, and applicable local regulatory requirements and laws in the states in which the study will be conducted. This study is posted on *http://www.ClinicalTrials.gov* (NCT03761277) as part of Medtronic's commitment to full disclosure for ongoing studies that meet the requirements for public posting.

The principles of the Declaration of Helsinki have been implemented through the patient informed consent process, IRB approval, study training, clinical trial registration, preclinical testing, risk-benefit assessment and publication policy.

Prior to enrolling subjects in this study, each study site's IRB will be required to approve the current CIP or CIP amendments, the subject ICF/HIPAA, including any other written information to be provided to the subjects and, if applicable, any materials used to recruit subjects. IRB approval letters must contain sufficient information to identify the version and/or date of the documents that were approved, or the information must be retrievable from the corresponding submission letter. Sites must also receive written approval of activation from Medtronic prior to initiating subject enrollments.

Investigators will be required to sign a Statement of Investigator Commitment form stating their intent to adhere to applicable regulations.

The sponsor shall avoid improper influence on, or inducement of, the subject, monitor, any investigator(s) or other parties participating in, or contributing to, the clinical investigation. All investigators shall avoid improper influence on or inducement of the subject, sponsor, monitor, other investigator(s) or other parties participating in or contributing to the clinical investigation.

16. Study Administration

16.1 Monitoring

Medtronic is responsible for ensuring the proper conduct of this study in terms of adherence to applicable regulations, protocol compliance, and the validity and accuracy of the study data entered on eCRFs. As such, investigational sites will be monitored to ensure the safety and well-being of study subjects is preserved, and to ensure site compliance with the study protocol, applicable regulations, and IRB requirements to ensure study data is accurate and complete.

Monitoring and monitoring oversight will be provided by Medtronic personnel or by representatives of Medtronic (i.e. contractors and other designees) who will support the study investigation including site qualification, site initiation, interim monitoring, and study closure visits.

Contact information for the study monitoring:

[redacted]

[redacted]

The PI and study staff will provide the Medtronic monitors with complete and direct access to source data (e.g., paper and electronic hospital/clinical charts, appointment books, laboratory records) that support the data on the eCRFs, as well as other documentation supporting the conduct of the study. Monitors will perform source data verification and routine reviews of study-related regulatory documents during scheduled monitoring visits and work to secure compliance should any deficiencies be observed. The monitoring plan contains the strategy for frequency of monitoring visits and source data verification to be performed for this study.

It is an expectation that the PI must make every effort to meet with the monitor during each monitoring visit.

16.2 Medtronic Representative Role

Medtronic representatives who are qualified and trained on the protocol may participate in the conduct of the study under the direct supervision of the PI as described below. The PI or other study site personnel designated on the delegation of authority form must collect all required data, record the study activities, and be responsive to the subject's needs during an activity performed by a Medtronic representative.

Medtronic representatives may provide technical support to the investigator and other health care personnel as needed during study visits. This support may include the training of site personnel on use of the Medtronic equipment or the protocol-related procedures and data collection.

In addition, Medtronic personnel may perform certain activities to ensure study quality. These activities may include:

- Provide technical support during IT trial, implant, and follow-up visits
- Perform device programming, while under the direction of the investigator or study site personnel delegated responsibility for device programming
- Discuss any issues with programming or subject compliance with the PI or other site personnel
- Clarify and/or troubleshoot device behavior, operation, or diagnostic output as requested by the PI or other health care professional
- Perform device interrogation, printing or uploading of device information while under the direction of the investigator or study site personnel delegated responsibility for the collection of study data from equipment and upload into the NPU database

Medtronic personnel may not perform the following:

- Practice medicine provide medical diagnoses or make decisions related to subject treatment/care

- Discuss a subject's condition or medical treatment with the subject or a member of the subject's family
- Express opinions about the product/feature under study
- Assist the subject by direct physical contact except as required by the specific protocol-related task to be conducted
- Provide the subject with any form/questionnaires related to the products under investigation
- Enter data on eCRFs, with the exception of the Medtronic Use Only fields/forms

16.3 Data Management

This study will use the Oracle Clinical RDC system, which allows the study centers to enter data directly on the eCRF within the sponsor's database over a secure internet connection. This system is a fully validated system and 21CFR§11 Part E compliant. The RDC system controls user access, ensures data integrity, and maintains an audit trail of entries, changes and corrections made to the eCRFs. User access will be granted by Medtronic to each applicable individual at a site based upon his or her delegation of authority for the study and only upon completion of the required training. The investigator and applicable study site personnel will be given access to the electronic eCRF system; user IDs and passwords may not be shared.

The PI is responsible for the completeness, accuracy and timeliness of the data entered on the eCRFs and the data in all other required reports. The PI or sub-investigator (physician only) must review all data for accuracy and provide his/her approval of the eCRF and sign each form with an electronic signature. Data reported on the eCRFs, must be derived from and consistent with source documents, unless otherwise stated in this section or the study monitoring plan. If discrepancies in source are identified during monitoring, these need to be corrected or a justification noted with a documented rationale, and then signed and dated by the PI, or authorized delegate, to be maintained as a part of the subject's records. If a person only authorized to complete eCRFs makes changes to an already signed eCRF, the system will require the PI, or authorized delegate, to re-sign the eCRF.

The eCRF may be considered the source for the following data collection elements:

- Investigator assessment of adverse event relatedness and seriousness
- Details pertaining to and reason for protocol deviation

Even when the eCRF may be considered as source (as noted above), an alternative method of source documentation is always strongly encouraged.

Medtronic personnel will perform routine edit and consistency checks, internally and during monitoring visits, for items such as missing data or inconsistent data. Identified data inconsistencies will be

resolved by use of data discrepancies within the RDC system; investigators and site personnel will review data discrepancies and respond to them in a timely manner. The resolved discrepancy will become a part of the eCRF record for the subject.

At the end of the study, the eCRF data will be frozen (locked) and will be retained indefinitely by Medtronic. Each subject's device programmer interrogation data will be stored in the NPU database.

16.4 Direct Access to Source Data/Documents

Source documentation is defined as the original documents, data and records and may include all clinical records, hospital records, laboratory notes, surgery reports, autopsy reports, and other documents, electronic or paper, that contain original information to support study data collections or AE reporting. The PI is responsible for ensuring source documentation is complete, legible, and accurate; and entries are made in a timely manner by appropriately delegated study staff.

The PI and site personnel will provide the Medtronic monitor(s) with direct access to source documentation or certified copies that supports the data on the eCRFs as well as other documentation supporting the conduct of the study.

Medtronic or third-party auditors representing Medtronic may perform clinical site audits to verify the performance of the monitoring process, study conduct, and to ensure compliance with applicable regulations. Representatives from regulatory bodies such as the FDA may also perform site inspections related to this clinical study. The PI, site personnel, and institution will provide monitors, auditors, and FDA with direct access to source documentation and all study-related documentation.

Medtronic will investigate all suspected cases of fraud or misconduct as appropriate.

16.5 Confidentiality

All records and other information about subjects participating in this clinical study will be treated as confidential. Subject confidentiality will be maintained throughout the clinical study to the extent permitted by law. For this purpose, a unique study-specific subject identification code (study - site - subject number) will be assigned and used to allow identification of all data reported to Medtronic for each subject. Subject confidentiality is assured through use of the study-specific subject identification numbers, use of initials only, and the de-identifying of subjects' records obtained by or provided to the Sponsor.

For purposes of monitoring this study, access to clinic and hospital records must be available to Medtronic, representatives of Medtronic (i.e. contractors and other designees), the FDA and other regulatory agencies. Study data may be made available to third parties (e.g., in the case of an audit or inspection performed by regulatory authorities), provided the data are treated confidentially and the

subject's privacy is guaranteed. The identity of a subject will never be disclosed in the event study data are published. Only anonymized data will be analyzed and published.

In addition to the review of records at the center, release of de-identified records to Medtronic may be necessary. The investigational site personnel must make every effort to de-identify and label source documentation with the subject's study-specific identification number prior to submission of the records to Medtronic.

Health Insurance Portability and Accountability Act (HIPAA) language will be required to be included at every center. HIPAA language may be included within the ICF, or separately, according to the center's policy.

16.6 Liability

The compensation and covered liability associated with this study conduct will be documented in a separate financial agreement signed by Medtronic, the PI, and/or the management of the study site/institution.

16.7 CIP Amendments

Protocol amendments may be initiated by Medtronic to address changes to the scope or conduct of the study. Protocol amendments, and associated documents, must be approved by Medtronic and submitted to the reviewing IRBs for approval prior to implementation except when necessary to eliminate an immediate or apparent immediate hazard to participating subjects.

16.8 Record Retention

16.8.1 Investigator Records

Documentation for this study will be produced and maintained to ensure that a complete history of the study exists. Documents created for this study, including all versions of original documents, will be identifiable and appropriately stored to assure control and traceability of data related to this study.

The PI is responsible for ensuring that all essential study documentation is retained and accessible for a minimum of 2 years (or longer as local law or facility administration requires) after the investigation is terminated or completed. The retention period may be longer if required by Medtronic, local or global regulatory requirements. Medtronic will be responsible for notifying sites of extensions to the 2-year minimum record retention requirements. Medtronic must be notified in writing by site personnel of any transfer of study documentation. The PI will ensure that essential study documents are not destroyed until written permission has been obtained from Medtronic or if allowed per contract.

At a minimum, the investigator is responsible for the preparation, review, submission to Medtronic and retention of all signed and dated case report forms, reportable adverse events, device deficiencies, subject deaths, deviations from the CIP. In addition, investigators are also responsible for maintaining all correspondence with another investigator, an IRB, the sponsor, a monitor, or FDA, related to this study (including approval documentation), records of each subject's case history and exposure to the device (including signed and dated informed consent forms & HIPAA authorizations, as well as source documentation of the consent process), final report, and all other study-related documentation.

16.8.2 Investigator Reports

The PI is responsible for the preparation (review and signature) and submission to the sponsor of all case report forms, adverse events, device deficiencies, deaths, and any deviations from the CIP. If any action is taken by an IRB with respect to this clinical study, copies of all pertinent documentation must be forwarded to Medtronic in a timely manner. Reports are subject to inspection and to the retention requirements as described above for investigator records.

Investigator reporting requirements for termination or suspension are listed in Section 16.10. The investigator shall prepare and submit in a complete, accurate and timely manner the reports listed in this section.

16.9 Publication and Use of Information

It is intended that study results will be published in scientific literature. Information provided related to patent applications, technical design, or manufacturing processes supplied to the investigator as a part of the investigational plan is considered confidential and is not to be included in publications without the consent of Medtronic. If required by a publisher, the PI agrees to obtain all necessary authorizations from study subjects prior to submitting study-related information for publication. Specific requirements regarding publication of study data will be provided in the study center agreement and in the publication strategy.

16.9.1 Publication Committee

Medtronic will form a publication committee to develop a publication strategy and to oversee the development and review of publications related to the study. The publication committee may include representation from physician study advisors, the designated participating investigators, and Medtronic. The publication committee will be responsible for overseeing and ensuring that the publication strategy is executed according to the established plan. Publication committee membership does not guarantee or provide privileges in terms of authorship.

The publication committee members will be responsible for reviewing all primary and secondary manuscripts prior to submission to the target journal and for reviewing abstracts prior to submission to conferences. In addition, publication committee members will review and approve requests for

secondary (ancillary) multicenter publications not included in the publication strategy. Requests will be reviewed to determine scientific validity, potential conflicts with previously submitted publications, and the need for Medtronic resources.

16.9.2 Authorship Selection

Authorship will follow the Ethical Considerations in the Conduct and Reporting of Research as defined by the International Committee of Medical Journal Editors (http://www.icmje.org).

16.10 Suspension or Early Termination

Early Termination is the closure of a clinical study that occurs prior to meeting defined endpoints. This is possible for the whole study or a single center. Suspension is a temporary postponement of study activities related to enrollment. This is possible for the whole study or a single center. Medtronic reserves the right to suspend or terminate the study or an individual study site at any time. In the event the study is terminated, the subject's devices will be programmed as per the investigator's discretion and once exited from the study, subjects will be managed by their physician.

16.10.1 Study-Wide Termination or Suspension

Medtronic reserves the right to suspend or terminate the study at any time. Reasons may include, but are not limited to, the following:

- Insufficient enrollment to complete the study within the expected timeframe
- Identification of adverse events or safety issues with the product or system that may impact the safety or welfare of study subjects
- Product performance/product supply issues

16.10.2 Investigator/Center Termination or Suspension

Medtronic reserves the right to suspend or terminate the study at an individual site. Reasons may include, but are not limited to, the following:

- Noncompliance with the protocol
- IRB approval lapse/expiration
- Serious or repeated deviations at the site
- Failure to implement required corrective and preventive actions
- Insufficient enrollment to complete the study within the expected timeframe
- Loss of appropriately trained site personnel
- Investigator request (e.g. no longer able to support the study)

Investigators are required to notify the IRB of study suspension/termination. Subjects will be notified by the investigator of suspension/termination due to unacceptable risk or of termination due to any other cause.

17. References

1. Wang JK, Nauss LA, Thomas JE. Pain relief by intrathecally applied morphine in man. *Anesthesiology*. 1979;50(2):149-51.
2. Onofrio BM, Yaksh TL, Arnold PG. Continuous low-dose intrathecal morphine administration in the treatment of chronic pain of malignant origin. *Mayo Clin Proc*. 1981;56(8):516-20.
3. Smith TJ, Staats PS, Deer T, et al. Randomized clinical trial of an implantable drug delivery system compared with comprehensive medical management for refractory cancer pain: impact on pain, drug-related toxicity, and survival. *J Clin Oncol*. 2002;20(19):4040-9.
4. LS S. Relieving pain in America: A blueprint for transforming prevention, care, education, and research. 2012.
5. Deer TR, Prager J, Levy R, et al. Polyanalgesic Consensus Conference--2012: consensus on diagnosis, detection, and treatment of catheter-tip granulomas (inflammatory masses). *Neuromodulation*. 2012;15(5):483-95; discussion 496.
6. Allen JW, Horais KA, Tozier NA, et al. Time course and role of morphine dose and concentration in intrathecal granuloma formation in dogs: a combined magnetic resonance imaging and histopathology investigation. *Anesthesiology*. 2006;105(3):581-9.
7. Allen JW, Horais KA, Tozier NA, Yaksh TL. Opiate pharmacology of intrathecal granulomas. *Anesthesiology*. 2006;105(3):590-8.
8. Yaksh TL, Hassenbusch S, Burchiel K, Hildebrand KR, Page LM, Coffey RJ. Inflammatory masses associated with intrathecal drug infusion: a review of preclinical evidence and human data. *Pain Med*. 2002;3(4):300-12.
9. Staats PS, Yearwood T, Charapata SG, et al. Intrathecal ziconotide in the treatment of refractory pain in patients with cancer or AIDS: a randomized controlled trial. *JAMA*. 2004;291(1):63-70.
10. Rauck RL, Wallace MS, Leong MS, et al. A randomized, double-blind, placebo-controlled study of intrathecal ziconotide in adults with severe chronic pain. *J Pain Symptom Manage*. 2006;31(5):393-406.
11. Wallace MS, Charapata SG, Fisher R, et al. Intrathecal ziconotide in the treatment of chronic nonmalignant pain: a randomized, double-blind, placebo-controlled clinical trial. *Neuromodulation*. 2006;9(2):75-86.
12. Hamza M, Doleys D, Wells M, et al. Prospective study of 3-year follow-up of low-dose intrathecal opioids in the management of chronic nonmalignant pain. *Pain Med*. 2012;13(10):1304-13.
13. Grider JS, Etscheidt MA, Harned ME, et al. Trialing and Maintenance Dosing Using a Low-Dose Intrathecal Opioid Method for Chronic Nonmalignant Pain: A Prospective 36-Month Study. *Neuromodulation*. 2016;19(2):206-19.
14. Smith TJ, Staats PS, Deer T, et al. Randomized clinical trial of an implantable drug delivery system compared with comprehensive medical management for refractory cancer pain: impact on pain, drug-related toxicity, and survival. *J Clin Oncol*. 2002;20(19):4040-9.

15. Hamza M, Doleys DM, Saleh IA, Medvedovsky A, Verdolin MH, Hamza M. A Prospective, Randomized, Single-Blinded, Head-to-Head Long-Term Outcome Study, Comparing Intrathecal (IT) Boluses With Continuous Infusion Trialing Techniques Prior to Implantation of Drug Delivery Systems (DDS) for the Treatment of Severe Intractable Chronic Nonmalignant Pain. *Neuromodulation*. 2015;18(7):636-48; discussion 649.
16. Deer TR, Prager J, Levy R, et al. Polyanalgesic Consensus Conference 2012: recommendations for the management of pain by intrathecal (intraspinal) drug delivery: report of an interdisciplinary expert panel. *Neuromodulation*. 2012;15(5):436-64; discussion 464-6.
17. Deer TR, Pope JE, Hayek SM, et al. The Polyanalgesic Consensus Conference (PACC): Recommendations on Intrathecal Drug Infusion Systems Best Practices and Guidelines. *Neuromodulation*. 2017;20(2):96-132.
18. Deer TR, Pope JE, Hayek SM, et al. The Polyanalgesic Consensus Conference (PACC): Recommendations for Intrathecal Drug Delivery: Guidance for Improving Safety and Mitigating Risks. *Neuromodulation*. 2017;20(2):155-176.
19. Deer TR, Hayek SM, Pope JE, et al. The Polyanalgesic Consensus Conference (PACC): Recommendations for Trialing of Intrathecal Drug Delivery Infusion Therapy. *Neuromodulation*. 2017;20(2):133-154.
20. Prager J, Deer T, Levy R, et al. Best practices for intrathecal drug delivery for pain. *Neuromodulation*. 2014;17(4):354-72; discussion 372.
21. Deer TR, Hayek SM, Pope JE, et al. The Polyanalgesic Consensus Conference (PACC): Recommendations for Trialing of Intrathecal Drug Delivery Infusion Therapy. *Neuromodulation*. 2017;20(2):133-154.
22. Deer TR, Pope JE, Hayek SM, et al. The Polyanalgesic Consensus Conference (PACC): Recommendations on Intrathecal Drug Infusion Systems Best Practices and Guidelines. *Neuromodulation*. 2017;20(2):96-132.
23. Deer TR, Pope JE, Hayek SM, et al. The Polyanalgesic Consensus Conference (PACC): Recommendations for Intrathecal Drug Delivery: Guidance for Improving Safety and Mitigating Risks. *Neuromodulation*. 2017;20(2):155-176.
24. Dunn KM, Saunders KW, Rutter CM, et al. Opioid prescriptions for chronic pain and overdose: a cohort study. *Ann Intern Med*. 2010;152(2):85-92.
25. [redacted]

18. Appendices

18.1 Appendix A: Additional Information for Sites

Detailed sponsor contact information not outlined in the Clinical Investigational Plan will be provided under a separate cover.

18.2 Appendix B: Institutional Review Boards

The table below represents all IRBs that were active at any time during the study. Information contained in this table is subject to change and will not require CIP revision.

IRB Name	Location	Leadership/Chair
WIRB Copernicus Group (WCG) IRB	1019 39th Ave., SE Suite 120 Puyallup, WA 98374	[redacted]
Eastern Virginia Medical School Office Research IRB*	721 Fairfax Ave. Suite 128 Norfolk, VA 23507	[redacted]
University of Texas Medical Branch Health IRB	301 University Blvd. Galveston, TX 77555	[redacted]
Lehigh Valley Health Network IRB*	1255 S. Cedar Crest Blvd. Suite 3200 Allentown, PA 18103	[redacted]

* Study was closed with the IRB under CIP V2.0

18.3 Appendix C: Participating Principal Investigators and Institutions

The table below represents all sites that were activated for participation, regardless of if they enrolled subjects or not.

Investigator Name	Institution / Site Name	Site Address
[redacted]	Northwest Pain Care	[redacted] Spokane, WA 99201
[redacted]	Premier Pain Treatment Institute	[redacted] Mount Orab, OH 45154
[redacted]	Coastal Pain and Spinal Diagnostics	[redacted] Carlsbad, CA 92009
[redacted]*	University of Virginia Pain Management Center	[redacted] Charlottesville, VA 22908
[redacted]	Regional Brain & Spine	[redacted] Cape Girardeau, MO 63701
[redacted]	The Pain Management Center	[redacted] Voorhees, NJ 08043

Investigator Name	Institution / Site Name	Site Address
[redacted]*	University of Texas Medical Branch	[redacted] Galveston, TX 77555-0591
[redacted]	Clinical Investigations	[redacted] Edmond, OK 73013-3023
[redacted]	Christian Hospital	[redacted] St. Louis, MO 63136
[redacted]*	Lehigh Valley Health Network Office of Research and Innovation	[redacted] Allentown, PA 18103
[redacted]*	Eastern Virginia Medical School	[redacted] Norfolk, VA 23507
[redacted]	Comprehensive and Interventional Pain Management	[redacted] Henderson, NV 89052
[redacted]	Moss Rehab - Einstein Healthcare Network	[redacted] Elkins Park, PA 19027
[redacted]	Florida Pain Institute Merritt Island	[redacted] Merritt Island, FL 32953
[redacted]	Precision Spine Care	[redacted] Tyler, TX 75701
[redacted]	Napa Valley Orthopaedic Medical Group	[redacted] Napa, CA 94558
[redacted]	Neuroversion	[redacted] Anchorage, AK 99508

* Site closed under CIP V2.0

19. Version History

Version	Summary of changes	Author(s)/Title
1.0	• Not Applicable, New Document	[redacted] Pr. CRS
2.0	Amendment 1 includes the following updates and clarifications: a. patients using cannabinoids (including cannabidiol) are excluded from the study b. patients must be on a minimum daily systemic opioid dose > 0 MME at the time of enrollment in the study c. psychological evaluation to be conducted per standard of care d. patient must have an MRI or CT and no clinical change in status since last imaging e. drug testing may be conducted using urine, blood, or oral fluid, per standard of care f. removed VAS, NOSE, and drug screen from the Implant visit g. confirm urine pregnancy test completed within 2 weeks prior to implant, per standard of care	[redacted] Pr. CRS
3.0	Amendment 2 includes the following updates: • Transitioned to 056-F275 CIP template vB • Updated language on study follow-up duration to include study exit at 6 months throughout (removal of 9 Month and 12 Month visits) • [redacted] • Entered final enrollment number of 93 subjects throughout • Inserted Section 8: Study Site Requirements in alignment with new CIP Template • Updated section 10.5 (Post-Op) to include “Initial and Final device interrogation reports” missed under V2.0 • Updated section 10.1, Table 2, section 10.7, and section 10.11 (Table 3) to remove reference to 9 and 12 month visits • [redacted] • Updated language in section 14.1.1 and 14.4.1 to correct the non-inferiority margin for VAS from 1 to 10 and to clarify sample size calculations • Updated section references throughout CIP	[redacted] Sr. CRS