Australian Government
Department of Health
Therapeutic Goods Administration

Medical Devices Program

Internal Form			
DCS FORM 1.a	Application Audit Clinical Assessment Report		
Comes under	DCDS SOP 1 Clinical assessment of application audit		
Applicable to	Devices Clinical Section	Authorised by	s.22 [redacted], DCS
Date issued	13 January 2021	Version #	1.0

Application details

To be completed by Clinical Section Reviewer

Submission ID	DA-2023-09130-1
Application ID	DV-2023-DA-27661-1
Sponsor name	Medtronic Australasia Pty Ltd
Manufacturer name	Medtronic Inc
Device classification	Class III
GMDN code and term	Analgesic spinal cord electrical stimulation system pulse generator implantable[64970]
Name of device(s)	Inceptiv Model 977119
Submission TRIM reference	E23-312815
Comments	See preliminary review (email): D23-3834192

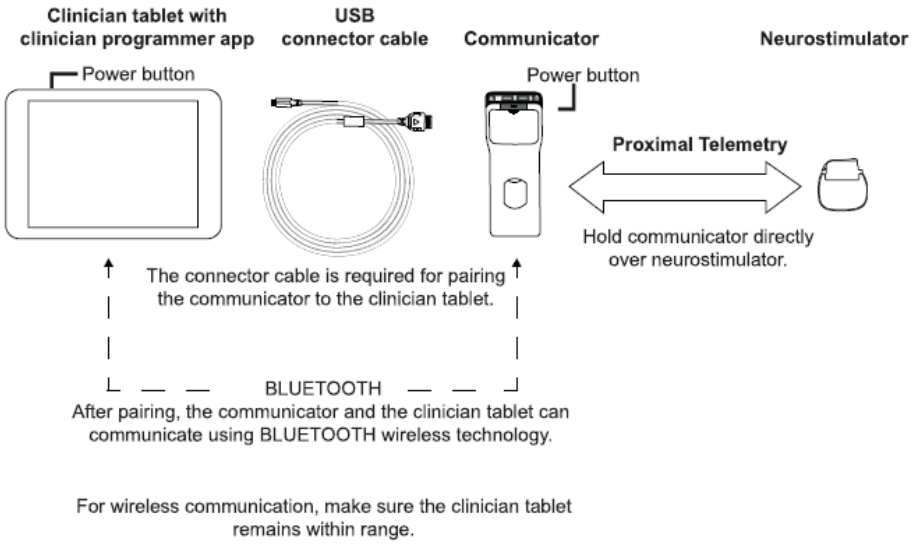
Device description

To be completed by Clinical Section Reviewer.

Clinical Reviewer to complete. If there are multiple applications or devices in the submission, add and complete a table for each application or device.

UPI	Components of the Pain RC system that includes the Inceptiv, Inceptiv LT and Intellis Pro rechargeable (RC) implantable neurostimulators (INS): • Stimulation RC Clinician Programmer Application, Model A71400 • MyStim RC Therapy Application, Model A72400 • Recharger Kit, Model RS7230
Device description	About the new INS in the RC Pain system, from CER (yellow highlight added): The new Pain RC neurostimulators offer the same Pain Stimulation therapy, with the same stimulation parameter options, for the same target population as the Model 97715/97716 Intellis system. The Pain RC neurostimulators are intended to replace the Intellis rechargeable neurostimulators (Models 97715 and 97716). They are compatible with existing Medtronic leads, extensions, adaptor extensions, communicators, and supporting programmer software. If necessary, the new Pain RC neurostimulators will use the Model B31060 Connector Plug Kit to cover an unused socket. The new Pain RC neurostimulators have new supportive devices, including clinician programmer applications, patient programmer applications, and a new recharger. One upgraded feature available on the Pain RC system (Model 977119 Inceptiv) is the Neuro Sense feature. The Neuro Sense feature is a closed-loop algorithm that controls stimulation by utilizing sensing of an evoked compound action potential (ECAP), which is a patient's physiological response to stimulation, to adjust stimulation output. When the Model 977119 Inceptiv device senses an ECAP with an amplitude greater than the threshold ECAP amplitude, pre-set by a clinician, the device reduces stimulation intensity to reduce overstimulation. The Model 977118 Intellis Pro and Model 977117 Inceptiv LT do not include this feature and are direct replacements for Model 97715 and 97716 Intellis neurostimulators, respectively. The feature set of the neurostimulators is determined by the clinician programmer application. <u>Stimulation RC Clinician Programmer Application, Model A71400</u> Used by clinicians to: • Program, adjust and troubleshoot compatible INS. • Program by selecting electrode contacts and adjusting the rate, pulse width and amplitude. • Review system related data such as neurostimulator usage, check lead connectivity/impedance and patient activity. There are three programming styles: • Legacy • Differential Target Multiplexed Spinal Cord Stimulation (DTM SCS) • Neuro Sense Only Inceptiv supports all three programming styles; Inceptiv LT supports Legacy only and Intellis Pro does not support Neuro Sense.

A71400 is used with Model CT900 Clinician Tablet, Model 8880T2 Communicator, Model A901 Communicator Manager application and Model A902 Patient Data Service application.



MyStim RC Therapy Application, Model A72400

Allows patients to:

- Control their stimulation, within clinician set limits, and turn their therapy ON and OFF.
- See their MRI eligibility status.
- Set their INS to MRI mode.
- Change settings for the Neuro Sense feature and DTM SCS programming, within clinician set limits, and to enable and disable the Neuro Sense feature is configured by the clinician.

A72400 is used with TM91 Communicator and Model HH90 Handset. The app is installed on the handset.

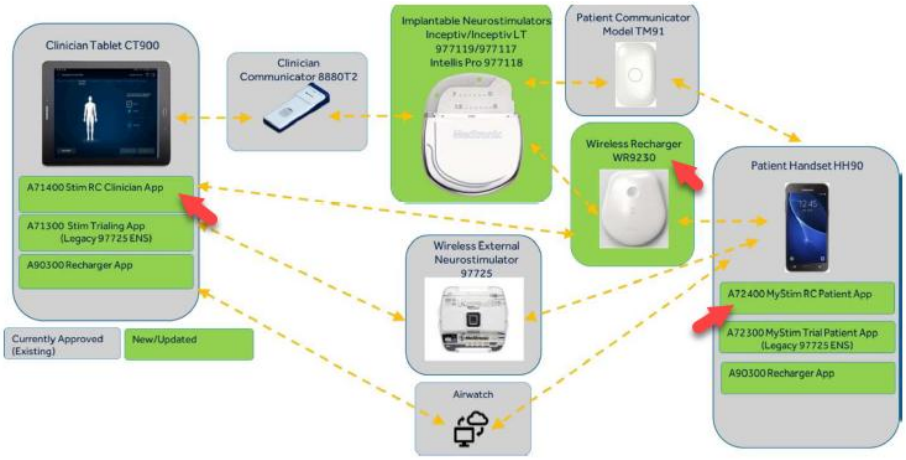
Recharger Kit Model RS7230

Components:

- Recharger Model WR9230
- Dock Model CD9000
- USB charging cable & AC power adaptor
- Carry case

Figure 2: Model WR9230 Recharger

Figure 3: Model CD9000 Dock – recharges the recharger WR923

Device configurations & variants	See below
System or procedure pack	Pain RC system, from the CER (with red arrows added for subject devices): 
Accessories or compatible devices	See above and CER (p.32-33)
Comments	Intended purpose (from eBS): The implantable neurostimulator generates electrical pulses and delivers stimulation through one or more leads as part of a neurostimulation system for pain therapy. When used as part of the Medtronic SCS neurostimulation system, the system is indicated as an aid in the management of chronic, intractable pain of the trunk and/or limbs associated with: ▪ Failed Back Surgery Syndrome ▪ Chronic back and/or radicular limb pain ▪ Complex Regional Pain Syndromes ▪ Diabetic Peripheral Neuropathy

Note: ***Unique product identifier (UPI)*** is only relevant for Class III/AIMD devices as it forms part of the "kind of medical device" by which these devices are entered in the ARTG. The UPI is given to the device by its manufacturer to identify the device and any variants. **Device name** is relevant to devices other than Class III/AIMD. For non-Class III/AIMD devices, the name of the device does not form part of the "kind of medical device" and is not recorded in the ARTG entry.

Scope of assessment

The aim of this assessment is to verify whether The Inceptiv Spinal Cord Stimulator and associated RC Pain System components comply with essential principles (EPs) 1, 2, 3, 4, 6, 13 and 14 from a clinical perspective.

Assessment

Clinical evidence report (CER)

Competency of CER author	The CER has been endorsed by s.22 , an appropriate clinical expert
Comments	The CER includes some evaluation of clinical data but it is not comprehensive, fair, or consistent. Data which is less favourable to the applicant is identified and then ignored, contrary to the explicit requirements of the TGA's *Clinical Evidence Guidelines* (see *Critical analysis and expert opinion*, page 35). For example, section 4.2.3.1 of the CER (*Performance Outcomes for Chronic Intractable Pain*, part of the *State of the Art* analysis) identifies a number of different performance measures described in the literature. The applicant simply fails to apply (or even mention) these standards where they are not met by the subject device. By way of illustration of the above point the performance of the device in terms of percentage pain relief observed in the PSR registry (see below) falls well below the lowest percentage described in the state of the art analysis. The clinical expert has responded by (apparently) simply not applying this standard and declaring that this was, "consistent with the range of performance outcomes identified in the SOTA literature (section 4.2.3.1)". Likewise, issues arise where the expert has nominated performance measures for the devices. The assessor is aware of the state of the literature with regards to minimally clinically important differences (MCIDs) and minimally clinically important changes (MCICs) in the literature for chronic pain. The CER consistently nominates benchmarks at the lower end of the range and fails to identify other MCIDs and MCICs.

Demonstration of equivalence ☒ Yes ☐ No

Comparator device	Medtronic's predicate *Intellis* system
Can the comparator device be considered substantially equivalent to the subject device based on clinical, technical and biological aspects?	☐ Yes ☒ No Comments: The CER provided describes a range of neurostimulators, only the *Inceptiv* Model 977119 is included in this application. Information to establish equivalence is provided only at a high level in sections 5.2.1 through 5.2.4 of the CER (sponsor reference NDHF1463-210919, TRIM reference D23-3311069).

A number of differences between the *Inceptiv* 977119 and the claimed substantially equivalent predicate were identified:

Clinically, the populations are “similar” rather than the “same”, this is framed around the *Intellis* having a broader intended population than the subject device, although it is noted by the assessor that the applicant proposes adding diabetic peripheral neuropathy as an indication for the subject device.

Biologically, the same materials are presented to the body.

Technically, the subject device uses a closed-loop algorithm with an automated programming template. The claimed substantially equivalent predicate did not feature closed loop programming. This is a very significant change, which directly alters the therapeutic output of the device in a way that is not replicable with the claimed substantially equivalent device.

> One upgraded feature available on the Pain RC system (Model 977119 Inceptiv) is the Neuro Sense feature. The Neuro Sense feature is a closed-loop algorithm that controls stimulation by utilizing sensing of an evoked compound action potential (ECAP), which is a patient’s physiological response to stimulation, to adjust stimulation output. When the Model 977119 Inceptiv device senses an ECAP with an amplitude greater than the threshold ECAP amplitude, pre-set by a clinician, the device reduces stimulation intensity to reduce overstimulation. The Model 977118 Intellis Pro and Model 977117 Inceptiv LT do not include this feature and are direct replacements for Model 97715 and 97716 Intellis neurostimulators, respectively. The feature set of the neurostimulators is determined by the clinician programmer application.

For this reason, while the data collected with the *Intellis* device could be informative, it will not be a substitute for direct clinical evidence with regards to efficacy.

Manufacturer’s clinical investigations

Has the manufacturer conducted clinical investigations?	☒ Yes ☐ No If no, what is the rationale and is this acceptable? *Comment on rationale and its acceptability*
Pre-market or post-market clinical investigations?	☒ Pre-market ☒ Post-market
Randomised controlled trial	☐ Device ☐ Predicate ☒ Nil **ECHO-MAC** Comments: The pre-market, randomized cross-over single-blind trial *ECHO-MAC* is described from pages 144-153 of the CER (sponsor reference NDHF1463-210919, TRIM reference D23-3311069). This study used a custom built “ECHO-MDT system” which replicates the closed-loop programming of the subject device to compare closed loop and open loop operation. The primary outcome (and only registered outcome) was self-reported over-stimulation. An unregistered secondary outcome of patient preference between the two modes was also reported.

The claimed function of the device (pain reduction) was not examined, based on the information provided in the CER, but this should be clarified with the applicant.

52 subjects were recruited out of 60 planned, with 42 analysed. The primary outcome was assessed using a 5 point Likert scale while undertaking 3-5 activities known to provoke overstimulation.

There was no follow-up and results were measured in a single session.

The results showed less overstimulation with the closed loop design, and most patients preferred the closed loop stimulation:

Table 35: ECHO MAC - Summary of Intensity Scores

Variable	Open loop	Closed loop	Paired difference (OL-CL)
Intensity score			
Measure Available	42	42	42
Mean (SD)	2.9 (0.8)	0.9 (0.8)	1.9 (0.9)
Median	3.0	0.8	1.8
Min to Max	0.5 to 4.0	0 to 2.8	-0.3 to 3.8

Table 37: ECHO MAC - Subject Preference

Subject preference	Number of subjects	Percent of subjects
Closed-loop	37	88.1%
Open-loop	5	11.9%
Total	42	100.0%

Notably the analysis indicates that “A clinical study is planned to evaluate the Neuro Sense feature with 24-month follow-up, as described in section 7.2, which will address these limitations.” An update will be requested to give the applicant the opportunity to present any efficacy data.

DTM-SCS

The DTM-SCS study was a post-market multicentre randomised controlled trial comparing the predicate *Intellis* device against itself in two different modes of operation, standard, and differential targeted multiplex (DTM).

The primary outcome was dichotomous response (defined as a 50% reduction in back pain VAS at 3 months). This was analyzed with a surprisingly broad non-inferiority margin of 10%. A very large number of secondary endpoints are also reported. Control for multiple comparisons is not described.

In any event, the broad non-inferiority margin was not consequential as there was an 80% responder rate in the DTM group, compared with 51% in the conventional stimulation group. 60% of patients had adverse events, 14% of patients had serious AEs, almost all of which were judged to be non-study related.

	Table 42 lists all study related AEs (12 in total), while table 43 lists those deemed as “serious” (2 in total, 1 case of site infection and one case of site pain). Notable one case of pneumocephalus was not deemed serious. Some caution is needed here, noting that the presence of pneumocephalus is something of a “red flag” finding and raises the possibility of ongoing leak from a dural breach, with the potential for longer term consequences including serious infection or symptomatic CSF leak.
Single-arm trial	☐ Device ☒ Predicate ☐ Nil Comments: **VECTORS** Comments: VECTORS was a post-market, single-arm multi-centre study and is described from pages 170-177 of the CER (sponsor reference NDHF1463-210919, TRIM reference D23-3311069). This study was designed to assess the degree of pain relief with high dose stimulation using the predicate *Intellis* device. Patient accountability is somewhat unclear, of 175 patients enrolled only 103 received implants. Figure 1 of the referenced publication (Hatheway et al, 2021) gives a patient flowchart, however it is difficult to interpret with classifications largely limited to identifying patient or clinician decision, or “other”. Of the 91 patients who attended 12 month followup very large effects were seen, for general, low back and leg pain improved (on average) 57%, 52% and 64% respectively, with 59%, 57% and 68% improving by 50% or more Of the 103 patients in the study there were 83 Adverse events post device activation in 43 patients:

Table 47: Vectors Study - Post-Activation Adverse Events Through Study Exit

MedDRA PT	No. of events	No. of serious events	No. of subjects with event	% of subjects with event (n=103)
Paraesthesia [a]	25	0	19	18.40%
Device stimulation issue [a]	14	0	11	10.70%
Back pain	11	1	10	9.71%
Medical device site pain	6	0	5	4.85%
Musculoskeletal pain	6	0	5	4.85%
Pain in extremity	5	0	5	4.85%
Implant site pain	2	0	2	1.94%
Pain	2	0	2	1.94%
Wound infection	2	0	2	1.94%
Abdominal pain	1	0	1	0.97%
Burning sensation	1	0	1	0.97%
Device dislocation	1	0	1	0.97%
Erythema	1	0	1	0.97%
Frequent bowel movements	1	0	1	0.97%
Gastrooesophageal reflux disease	1	0	1	0.97%
Lead dislodgement	1	0	1	0.97%
Medical device site cellulitis	1	0	1	0.97%
Musculoskeletal discomfort	1	0	1	0.97%
Post procedural discharge	1	0	1	0.97%
Total	**83**	**1**	**43**	**41.70%**

[a] When combined into the more general category of "Uncomfortable stimulation including paresthesia", the 39 events of "Paraesthesia" or "Device stimulation issue" occurred in 28 (27.2%) subjects.

Other

☐ Device ☒ Predicate ☐ Nil

Comments: Results from the sponsor's internal device registry *Product Surveillance Registry* (PSR) begin on page 177 of the CER. This registry includes multiple devices. For the purpose of this CER the sponsor has extracted data only for the predicate *Intellis* device.

The data contained is an appropriate mixture of pain, disability and quality of life outcomes at a number of clinically appropriate time points, these include:

- Visual analogue scale for pain (general)
- Visual analogue scale for pain (back)
- Visual analogue scale for pain (leg)
- Oswestry Disability Index
- EQ-5D-UK/EQ-5D-VAS

Multiple centres participated within the registry, but the registry captures only a very small fraction of total device usage. s.47 neurostimulators were captured in [redacted] unique patients by the 31st of July 2021. (More than s.47 [redacted] have been sold in the sales data attached to the report).

The data is substantially “real world” without restrictive inclusion criteria, capturing all patients with on-label usage. s.4 patients were excluded for off-label usage (angina, facial pain, and migraine). The remaining [redacted] patients have [redacted] total years of follow-up. The indications were as follows:

Table 52: PSR - Primary Treatment Indications for Intellis Patients

Primary Treatment Indication*	Enrolled Patients (%)
Failed Back Pain	[redacted] (54.08%)
Combination Back and Leg Pain	[redacted] (21.10%)
Failed Back Surgery Syndrome (FBSS)	[redacted] (20.68%)
Post Laminectomy Pain	[redacted] (10.55%)
Multiple Back Operations	[redacted] (1.65%)
Unsuccessful Disc Surgery	[redacted] (0.10%)
Other Primary Indication	[redacted] (36.71%)
Radicular Pain Syndrome	[redacted] (16.24%)
Degenerative Disc Disease	[redacted] (6.20%)
Other Chronic Pain	[redacted] (4.76%)
Traumatic Nerve Injury	[redacted] (0.93%)
Diabetic Neuropathy	[redacted] (0.52%)
Other	[redacted] (8.07%)
CRPS	88 (9.10%)
CRPS I	[redacted] (7.24%)
CRPS II	[redacted] (1.86%)
Not Specified	[redacted] (0.10%)
Total Patients	[redacted] (100%)
* For approved indications refer to product labeling for your geography.	

The performance data reports only outcomes from patients receiving their first stimualtor, and not those replacing an existing stimulator. This is appropriate.

A large number of patients were captured, and the number of patients included in the PSR is greater than the number included in all preclincial studies combined. Numbers drop off substantially between 12 and 24 months however it is not clear whether this represents loss to follow up, or a ramp up in inclusion between 24 and 12 months before the cutoff date.

The performance data is substantially worse than the performance in the manufacturer’s published studies.

At 12 months the average improvement in general pain (from s.47 patients who had measures at both time points) was 1.4 from a baseline of 6.5, or an average improvement of 21.5%.

	At 12 months the average improvement in back pain (from s.47 patients who had measures at both time points) was 1.7 from a baseline of 6.6, or an average improvement of 25.7%. At 12 months the average improvement in leg pain (from [redacted] patients who had measures at both time points) was 1.9 from a baseline of 6.1, or an average improvement of 31%. At 12 months the average improvement in ODI (from [redacted] patients who had measures at both time points) was 8.7 from a baseline of 50.9, or an average improvement of 17%. At 12 months the average improvement in EQ-5D-VAS (from [redacted] patients who had measures at both time points) was 2.9 from a baseline of 59.6, or an average improvement of 4.8%. When analysis is restricted to patients with a baseline general pain score of 5 or more results are virtually identical (see table 56) in percentage terms, but unsurprisingly yield slightly higher changes when dominated in points. Table 57 (CER pages 185-186) indicates 18 adverse events per 100 patient years, with 11.6% of patients having at least one event with an average of 13 months follow-up. **Evidence Relating to the Treatment of Diabetic Peripheral Neuropathy** The applicant proposes adding diabetic peripheral neuropathy as an indication for therapy. This is supported solely by data from the PSR registry. Only [redacted] patients total were implanted with the predicate Intellis device with an indication of diabetic peripheral neuropathy. (The applicant also provides a second analysis of a further [redacted] patients who had diabetes and leg pain without an indication of peripheral neuropathy, however given it is unclear if any of these patients had the condition being treated these are non contributory.) A retrospective cohort of [redacted] people is not adequate to assess the safety of the device. Of the [redacted] patients included, average follow-up was approximately [redacted] year and there were [redacted] product performance events in [redacted] patients. These numbers are too small to meaningfully compare to overall rates. Three patients reached 12 month follow-up with general pain, and had only modest change in pain (a reduction of 1.3 points on a baseline of 6.7 points, a reduction of 19%). No patients reached 12 month follow-up with back or leg pain. This is obviously inadequate to support regulatory approval.
Investigation scope and design	There are readily apparent difficulties in providing a single overarching assessment of the data above, principally the substantial inconsistency between the published studies (showing reasonable efficacy) and unpublished data (showing poor efficacy).

Published studies in support of the device (and *Intellis* predicate) are small with weak designs. While the clinical evidence guidelines require studies for implantable pulse generators to be “study designs to the highest practical NHMRC Level of Evidence” this is not the case here.

The applicant submits four sources of data

- The DTM SCS trial
- The ECHO-MAC trial
- The VECTORS study
- The unpublished PSR registry.

ECHO-MAC does not report any efficacy outcomes of interest (as defined by the applicant in section 3.11.1 of the CER “Intended clinical benefit to patients”)..

DTM-SCS reports only back pain, with a 67% reduction at 6 months in the DTM arm and 47% in the conventional programming arm.

VECTORS reports improvements of 57%, 52% and 64% at 12 months for general pain, back pain and leg pain specifically.

The PSR registry is by far the largest source of data, and presents “real world” effectiveness (albeit at individually selected hospitals and with off label use excluded). These results are very concerning and conflict with the study results.

In s.47 patients at 12 months, general pain showed only a 22% improvement, less than half the lower limit of the range identified in the applicant’s definition of State-of-the Art (44% to 72% improvement), and approximately a third of the improvement seen at the same time point on the same measure in the published VECTORS study (57%).

Similar patterns were seen for back and leg pain.

Adverse events across all sources of data when denominated by patient years were large, from 18 per 100 patient years in the PSR registry to approximately 92 per 100 years in the VECTORS study (based on 83 events in 1166.4 patient-months following device activation and 9 events in 1288 patient-days of followup between device implantation and activation per tables 44 and 47).

Overall the data presents two conflicting pictures of device performance, in manufacturer studies which have been published or which the manufacturer intends to publish the device appears to be moderately to highly effective, reducing pain by approximately 50-70% at 12 months. In the larger real-world dataset which the manufacturer has collected but not published the device performs poorly, with reductions in pain in the range of 20-30%. These differences are summarised in table form on page 12 of this report. For all specified pain types, the percentage improvement at 12 months in the unpublished registry:

- is worse than the lower limit of the state of the art defined by the applicant

- is worse than the worst published result in any published study or public facing material identified by the manufacturer.

The improvements are so small that it is unclear whether these actually constitute a “benefit” at all. MCICs for chronic pain in the literature vary by large amounts. The described changes are smaller than those reported in many large studies, although would be just above the lowest estimates in some studies.

One piece of information not provided is responder rates from the PSR data set. Noting that these are planned in the methodological description it seems reasonable to assume these exist, and a request for the same will be recommended.

In any case, it is clear that the sponsor holds substantial high-quality data that the devices, when used in clinical practice, perform very substantially worse than is described in sponsored studies and manufacturer marketing material based thereon. No plan to disclose this to patients or prescribers is identified. This prevents a conclusion that the device conforms with EP 13. Based on the very small magnitude of clinical improvement it is unlikely the device conforms with EP 1, however review of responder rates would be prudent before reaching a final conclusion. Based on the substantial risk profile of this device as described above, unless very substantial benefit can be established, accepting conformity with EP 6 is also unlikely.

Data source	ECHO-MAC (nil pain outcomes)		DTM-SCS (test arm, 6 months)		DTM-SCS (Conventional, 6 months)		VECTORS (12 months, "treated analysis set")		PSR (12 months, all patients)		State of the Art (from applicant's CER)	
	N	% change	N	% change	N	% change	N	% change	N	% change	Lower limit	Upper limit
General Pain	-	-	-	-	-	-	103	57%	s.4	22%	44%	72.3%
Back Pain	-	-	46	67%	58	47%	103	52%		26%	42%	69%
Leg Pain	-	-	-	-	-	-	103	64%		31%	52%	73%

This table shows percentage improvement in each of "general pain", "back pain" and "leg pain" at 12 months across all clinical data sources provided by the applicant.

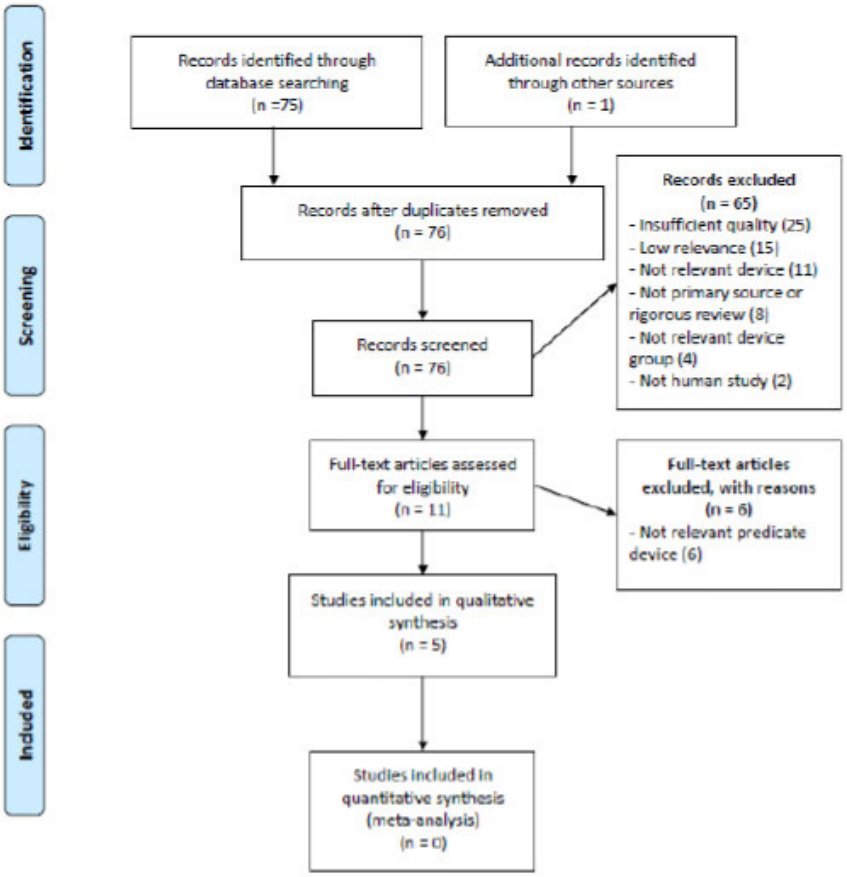
Note 1: Data from DTM-SCS is at 6 months

Note 2: Data from VECTORS is on an ITT basis and N includes patients lost to follow up.

Clinical literature review ☐ **Yes** ☐ **No**

Literature search protocol provided	☒ Yes ☐ No Comments:
Selection criteria of the literature review	☐ Device ☒ Predicate ☐ Similar marketed ☐ Addresses all device variants (if any) in the device application ☒ Addresses the same clinical condition
Literature type	☒ Published literature ☐ Unpublished literature ☐ Other
Data appraisal	The literature search was limited to the predicate intellis system. A 4 year period of 2017 to 2021 was selected. A separate document outlining the search strategy in greater detail (NDHF1463-208456) is referenced but not provided. 75 citations were returned. 5 were deemed suitable for inclusion by way of qualitative analysis. 0 were deemed suitable for inclusion in a quantitative synthesis (meta-analysis)

A PRISMA flowchart is provided on page 155 and reproduced here:



Of the five papers which receive qualitative analysis:

- 1 is the published report of the VECTORS study described in the section above
- 3 are repeat analyses of the DISCOVER study (by the same author). Discover was an observational prospective multi-centre single-arm study in Europe of high dose SCS for failed back surgery syndrome. It was funded by the sponsor. 194 participants were enrolled and 92 reached the 12 month followup. This makes the results difficult to generalize. Participants on average (for those reaching 1 year followup) had a 54% improvement in leg pain and a 41% improvement in back pain.
- 1 is a retrospective case series of 38 patients from Palermo. Funding is not disclosed. This case series reports irregularly, and does not follow a standard structure. Dichotomous “success” is reported based on a pain score of less than 3, regardless of preoperative severity. No time period is specified. Given that no pain outcomes are reported in a way that overlaps with any reporting from any other source this paper does not represent usable information.

Overall, the literature review adds little, with the exception of the single DISCOVER paper which reports pain outcomes. The generalizability of these results is difficult to ascertain given that a majority of patients were lost to attrition (including loss to follow-up, voluntary decision not to proceed despite success trial, infection etc).

Other clinical experience ☒ **Yes** ☐ **No**

Adverse events with complaint rates	☐ Device ☒ Predicate ☐ Nil Comment: Complaint and vigilance data is collected in appendix E through G of the CER. These are up to date only until April 2021. Rates of "non-serious" complaints were very high, with approximately s.47 complaints received for the 97715 *Intellis* model (table 82) at a time when only s.47 devices were in use world-wide (table 81).

Reporting Period: Current Period (01-MAY-2020 to 30-APR-2021) and Cumulative Period (01-MAY-2017 to 30-APR-2021)		Non-Serious Complaints							
		Current Period				Cumulative Period			
		Count		Rate		Count		Rate	
Device Name	Reason for Report (RFR) Description	EU	WW	EU	WW	EU	WW	EU	WW
97715 Intellis INS Adaptive Stim	NO IDENTIFIED PRODUCT ISSUE	5	1612	0.058%	2.159%	8	4138	0.023%	1.386%
97715 Intellis INS Adaptive Stim	INS ISSUE / BATTERY DISCHARGE OR DEPLETION OR EOS OR ERI / RECHARGEABLE BATTERY ISSUE	12	1579	0.139%	2.115%	36	3541	0.104%	1.186%
97715 Intellis INS Adaptive Stim	SYSTEM OR USE ISSUE / RECHARGING ISSUE / RECHARGING OF INS ISSUE	9	1493	0.104%	2.000%	43	4205	0.125%	1.408%
97715 Intellis INS Adaptive Stim	SYSTEM OR USE ISSUE / ERROR CODE OR WARNING MESSAGE OR DIAGNOSTIC MESSAGE DISPLAYED / PATIENT CONTROLLER (INTELLIS)	8	1151	0.093%	1.542%	35	3442	0.102%	1.153%
97715 Intellis INS Adaptive Stim	SYSTEM OR USE ISSUE / STIMULATION OUTPUT ISSUE / UNEXPECTED CHANGE IN OUTPUT	12	1119	0.139%	1.499%	38	3419	0.110%	1.145%
97715 Intellis INS Adaptive Stim	SYSTEM OR USE ISSUE / ENVIRONMENT ISSUE / PHYSICAL FORCE OR ACTIVITY AFFECTED IMPLANTED SYSTEM	2	433	0.023%	0.580%	6	1349	0.017%	0.452%
97715 Intellis INS Adaptive Stim	SYSTEM OR USE ISSUE / COMMUNICATION OR TELEMETRY ISSUE / NO COMMUNICATION OR FAILURE TO INTERROGATE	8	407	0.093%	0.545%	29	948	0.084%	0.317%
97715 Intellis INS Adaptive Stim	SYSTEM OR USE ISSUE / IMPEDANCE ISSUE / HIGH IMPEDANCE	7	392	0.081%	0.525%	17	1024	0.049%	0.343%

Many of these have the potential to impair device function. Careful consideration of the definitions applied by the sponsor to determine that these were non-serious will be required. If these complaints include patients who lost full or partial function in their devices, then the rates expressed may not be compatible with a finding of conformity with EP1.

Total serious incident rates are much smaller, with only "unspecified infection" at or greater than 1 in 1,000 (0.126%), all other rates appear in line with accepted complications of spinal cord stimulators.

Public adverse event databases	☐ Device ☐ Predicate ☐ Similar marketed ☒ Nil Comment: *Describe data/information and any significant issues.*
Recalls (or actions such as market withdrawals, field corrections, safety alerts)	☐ Device ☐ Predicate ☐ Similar marketed ☒ Nil Comment: *Describe data/information and any significant issues.*

Corrective and preventative actions (CAPAs)	☐ Device ☐ Predicate ☒ Nil Comment:
Registry data	☐ Device ☒ Predicate ☐ Similar marketed ☐ Nil Comment: See above, included as “PSR”. This is a multi-site registry, but which has captured less than 1% of devices sold to date, differing substantially from comprehensive national registries
Other	☐ Device ☐ Predicate ☐ Similar marketed ☒ Nil Comment: *Describe data/information and any significant issues.*
Comments	*Comment on any issues with the clinical experience data/information*

Risk management

From a clinical perspective, does the report/FMEA include the risks arising from the use of the device for its intended purpose, and foreseeable misuse of the device?

☒ Yes ☐ No

Comments: Risk management reports were provided separately by the sponsor, see the attachment to trim link D23-3649319. The relevant hazard analysis is on a whole-of-indication basis (see bookmark 1.01) and includes both SCS and PNS. (With the exception of the programmer application which has its own hazard analysis).

The risk management reports are on a whole-of-system basis with 1.04 being the most relevant. Again, software applications are reported separately at 1.05-1.06

While the hazard analysis, estimates and controls appear reasonable, a number of hazards remaining at a high absolute risk, and have been accepted on a reduced as-far-as-possible basis:

Table 1: Inherent surgical, procedural or therapy Residual Risks for the SCS Chronic Implant System

Probability of Occurrence of Harm (P)	Harm Severity Categories				
	Negligible - 1	Minor - 2	Major - 3	Critical - 4	Catastrophic - 5
Frequent - 5	0	0	2	1	0
Probable - 4	0	0	2	0	0
Occasional - 3	0	0	2	2	2
Remote - 2	0	0	1	0	2
Improbable - 1	0	0	0	0	0

This is described by the applicant in the following terms:

	SCS Chronic Implant System: The Chronic Implant section of HA NDHF1555-159439 includes the following Zone 3 risks: • Inherent clinical side effect under normal conditions (procedure or system related) (CLIN-439-1, CLIN-439-2, CLIN-439-3, CLIN-439-4, CLIN-439-7, CLIN-439-8, CLIN-439-9, CLIN-439-10a, CLIN-439-10b) These hazards capture the inherent clinical risks associated with use or implant of the SCS system for chronic implant. This includes exposure to surgery, potential surgical complications (e.g. infection, hematoma, spinal cord injury, spinal cord compression, CSF leak) and potential ambulatory effects (e.g. delayed spinal cord compression, erosion). Labeling notifies the clinician of the potential of these risks. Medical Safety Assessments REG31093, REG10945, REG36164, REG28699, REG39084, REG42932, REG28317, REG41737, REG30552, REG23330, and REG42821 were created to assess risks associated with INS inversion, formation of reactive tissue, trauma, undesirable physiological response (urinary and gastrointestinal symptoms), CSF leak, and neurological deficit. This is not incorrect, noting that inherent risks of a surgical procedure can only be reduced so far, and that death is a recognised complication of surgical procedures under anaesthetic. However, acknowledging that critical risks occur frequently and catastrophic risks occur occasionally raises the bar for the level of benefit which must be demonstrated to show compliance with EP 6. One risk which needs further explanation was the addition of “delayed spinal cord compression” at version 7. It will be important to understand whether this was an addition from theory (it is reasonable to consider that introducing any foreign body through the highly vascular extradural space risks such a complication), or from an actual signal.
Do the risks associated with the use of the device appear to have been adequately mitigated?	☒ Yes ☐ No Comments: Yes, noting the above limitations arising from the need for surgical implantation.
Are the residual risks appropriately documented in the IFU/labels/PIL?	☐ Yes ☒ No Comments: The manual (D23-3671850) contains a sentence saying: > ! USA **The clinical summary provides information about the clinical study results for the neurostimulation system.** but otherwise does not mention risks. The other document labelled “IFU” (D23-3672024) contains only a list of indications

Safety in Magnetic Resonance (MR) environment

☒ Active implant ☐ Passive implant ☐ Not implantable

MR safety labelling claim	MR Conditional If MR Conditional, specified conditions of use: A separate "MRI Guidelines Manual" is referenced regarding acquisition parameters. This has not been provided in full but the relevant excerpts are on page 75 of the TDAR. **Implanted components and MRI scans** **Implant criteria for full-body MRI scan eligibility** **Caution**: To allow a patient full-body MRI scan eligibility under specific conditions, implant a Medtronic neurostimulation system with SureScan MRI technology as follows: ▪ Use only SureScan MRI neurostimulation system components (eg, leads and neurostimulators). **Note**: Implanted systems that include either extensions or adaptors are not full-body MRI scan eligible. ▪ Implant the neurostimulator in the buttocks, abdomen, or flank (ie, the lateral and posterior region between the ribs and pelvis). ▪ Place the lead tip(s) in the spinal epidural space. ▪ Explant any previously abandoned pain leads or extensions that may be in the patient (ie, leads or extensions, or portions of, that are not connected to a neurostimulator). **Note**: Confirm MRI compatibility of any other implanted medical devices. Other implanted medical devices may limit or restrict MRI scans. ▪ Enter all component model number and implant location information using the clinician programmer. If the above implant criteria are not met, the patient will not have a neurostimulation system with full-body MRI scan eligibility. MRI scan eligibility will be restricted. For the MRI conditions and MRI-specific warnings and precautions for conducting an MRI scan, refer to the *MRI guidelines for Medtronic neurostimulation systems for chronic pain* instructions for use manual. MR scans performed under different conditions can result in patient injury or damage to the implantable device.
Overall, does the evidence provided support the MR safety claims in the IFU/labels/PIL?	☒ Yes ☐ No Comments: Relevant source reports have not been provided, but were reviewed and found acceptable by the Notified Body as part of MDR certification. Given that the final parameters specified appear reasonable, and that the Notified Body explicitly assessed these against an accepted standard, and that this is an MDR supported application, and that the assessor has no specific concerns, the source documents do not need to be requested from the applicant. Protection of the device from electromagnetic non-ionizing radiation (EN 45502-1:2015 & ISO 14708-1:2014 Cl. 27.1): • NDHF1588-203802 Ver 2.0 NGRC (Model 977117, 977118 & 977119) EMC #1, DVT Test Report • NDHF1588-203806 Ver. 2 NGRC (Model 977117, 977118 & 977119) EMC #2, DVT Test Report **Evaluation** The requirements of the MDR, and if applicable CS, are fulfilled ☒ Yes ☐ No **6.1.7 MRI safety testing of the device / device system (MDR Annex II Section 6.1(b))** GSPR 14.2(b), 18.5: The MRI safety of the devices is adequately addressed by the manufacturer ☒ Yes ☐ No ☐ n/a Please see section 6.1.8 and section 6.1.9 for further details

IFU, labels and other information provided with the device

From a clinical perspective, does the information provided with the device (IFU, labels, PIL, etc.) provide adequate information on the intended purpose, proper use, and warnings about risks to patients and users?	☐ Yes ☒ No Comments: As above, the technical manuals provided to date are missing essential information such as the communication of risks to prescribers, because they contain a reference to an external “clinical guide”. This is marked as “USA only”. The applicant should clarify they have submitted the correct IFU.

Assessment summary

The device system under examination is a rechargeable spinal cord stimulation system which the applicant states is planned to replace the applicant’s existing *Intellis* systems. The applicant claims equivalence to the *Intellis syst*em. The device is not substantially equivalent as the subject device offers “closed loop” stimulation which was not present on any predicate device.

The applicant has conducted a single pre-market study comparing open to closed loop stimulation using a custom trial stimulator rather than the subject device. This study (ECHO-MAC) consists of 44 patients attending a single clinical visit with no follow-up, who were randomised to have either closed or open-loop stimulation first and then cross over. The study recorded both subjective degree of overstimulation (less in the closed loop group), patient preference (more for closed loop), and amplitude of evoked action potentials (substantially smaller in the closed loop group). No efficacy outcome, as defined in the CER by the applicant, was reported. This does not establish non-inferiority against the predicated open loop system. The applicant should be asked whether pain relief was recorded.

Putting to one side issues of equivalence, the data presented for the *Intellis* device is highly concerning. Sponsored studies intended for publication, including DTM-SCS and VECTORS describe a highly effective device, with reduction in pain (general, back or leg) of 50-70%. These are either single arm studies or RCTs of the same device against itself in different modes. These results all fall within the bounds of percentage improvement in the State of the Art defined by the applicant. However, the applicant has also disclosed the existence of an internal registry which described real world usage of the *Intellis* in s.47 . This data does-not appear to be intended for publication and the assessor cannot find any evidence of it having been disclosed to prescribers or patients. This data tells a remarkably different story. Of patients who the sponsor deemed as being “on label usage”, the reductions in pain seen were only a small fraction of what the for-publication literature would suggest. General pain at 12 months was reduced by only 21%, back pain by 26% and leg pain by 31%. All of these results are substantially below the lowest limit of the state of the art range described for the respective pain types at 12 months. The applicant should be asked to clarify how and if this data is intended to be disclosed to prescribers. If the applicant intends to not disclose this information then conformity with EP 13 is likely impossible. Even if communicated, it is unclear that a device with such modest changes to perceived pain conforms to EP 1.

The analysis of this data provided in the CER does not meet the requirements of the clinical evidence guidelines. The report does not give due consideration to data that is unfavourable. For example the applicant has ignored the fact that the level of improvement seen in patients in the PSR falls very substantially below the level of improvement defined in their own state of the art analysis. The applicant has done this by:

- Selective extraction, the applicant has chosen, when compiling effectiveness outcomes in table 66 of the CER, to analyse only those patients in the high-baseline-pain subgroup of the PSR data set and ignored the all-on-label analysis set completely.
- Selective application, the applicant has defined percentage improvement ranges in the state of the art review, then simply ignored them in analysing clinical data such as the PSR data set (noting that the percentage improvement seen was well below the lowest limit in all cases)
- Selective identification, the applicant has selected an MCID from the literature which is at the low end of the range (a single result from Farrar et al), despite the fact the authors warn against its use for outcomes longer than 12 weeks. This MCID (1.7) falls just under the range of results seen in the chosen subgroup analysis (1.8). Curiously this is a new addition that was not present in the *Intellis* CER, so it will need to be clarified with the applicant whether this was chosen after the results were already known (July 2021).

The applicant proposes an extension of indication to include Diabetic Peripheral Neuropathy, the evidence is clearly insufficient, with only a retrospective cohort of 27 patients with the predicate device and diabetic peripheral neuropathy identified. Only 3 patients had 12 months followup or more.

The risk management report and other sources (including the PSR registry) indicate that adverse events are common, occurring in 40% of patients in the first year of the VECTORS study and 11% in the PSR register. The risk management report describes catastrophic risks occurring occasionally and critical risks occurring frequently as inherent risks relating to the implant procedure. Given the above it is not clear that the device complies with EP 6.

The adequacy of the submitted Instruction for Use Documentation is unclear as it is not clear the applicant has submitted the correct documentation. The Manual (which acts as the IFU) does not contain appropriate clinical warnings, but instead refers to an additional document which is marked “USA only”

Finally, the complaint rate is very high, with 22,000 complaints received at a time when 76,000 devices had been sold. While “non-serious” many would seem to interfere with device function, and more detail is needed to consider conformity with EP 1.

Conclusions and recommendations

Clinical assessor’s conclusion and recommendation

Following assessment of the information provided for this application audit in relation to the Inceptiv SCS, it is recommended that the sponsor be requested to provide the following:

Further information is required to establish whether the device complies with the essential principles, especially essential principles (EP) 1, 2, 3, 4, 6, 13, 13a and 14:

1. A full study report of the ECHO-MAC study, to contribute to the assessment of compliance with EP 3, 6 and 14.
    a. Please explicitly state whether patient pain (via any validated instrument, NRS, VAS, etc) was measured
2. The claim of equivalence between the subject device and *Intellis* system is not currently sufficiently supported. Noting that the move to closed-loop stimulation is a substantive change in the therapy delivered, please indicate whether the applicant holds evidence of non-inferior performance, the follow-up duration of such data, and please submit any such data, to contribute to the assessment of compliance with EP 14.
3. Please indicate whether the pain improvement threshold (from Farrar et al) was selected as a result of a formal selection process. Provide a justification for the selection of this source in selecting from the many available MCIC/MCIDs in the literature, to contribute to the assessment of compliance with EP 6 and 14.

4. Please indicate whether any interim analyses of the NeuroSense study described in section 7.2 of the CER are available, to contribute to the assessment of compliance with EP 14
5. For the patients in table 54 of the CER, to contribute to the assessment of compliance with EP 3, 6 and 14:
    a. Please indicate how many of the 215 patients with 12 month change scores for general pain
        i. Improved by 50% or more
        ii. Improved by 80% or more
    b. Please indicate how many of the 170 patients with 12 month change scores for back pain
        i. Improved by 50% or more
        ii. Improved by 80% or more
    c. Please indicate how many of the 151 patients with 12 month change scores for leg pain
        i. Improved by 50% or more
        ii. Improved by 80% or more
6. Please indicate whether the applicant plans to publish the results in table 54 of the CER (containing the PSR change in pain results), or if not, whether the applicant plans to communicate the same to patients and prescribers, to contribute to the assessment of compliance with EP 13.
7. In table 66 of the CER, the author has extracted pain change scores from the PSR in the subgroup with more severe baseline pain (table 56), rather than all on-label usage. Please indicate whether the applicant is seeking to include a minimum score in the proposed indication, to contribute to the assessment of compliance with EP 3 and 14.
8. The data in support of adding diabetic peripheral neuropathy falls well short of what is required, please indicate if the applicant would like to submit any further data in support of this indication, to contribute to the assessment of compliance with EP 14.
9. Document NDHF1555-159439 refers to a product issue assessment for delayed spinal cord compression. Please indicate whether this arose from a safety signal or was a theoretical risk identified on routine review, to contribute to the assessment of compliance with EP 1, 2, and 4.
10. Table 82 describes a very high rate of “non-serious” complaints. Please indicate whether loss of device function was a criterion for determining seriousness and reasonable to assume that none of the complaints in this table results in a loss of device efficacy, to contribute to the assessment of compliance with EP 1, 2, 3 and 4.
11. The attached “implant manual” does not contain any information about adverse events, please indicate if a separate IFU document contains these and submit the same, or a modified version of the existing documents, to contribute to the assessment of compliance with EP 13A.
12. Information provided on the proposed PMCF is not sufficiently detailed. Please provide details including the outcomes of interest, the baseline demographic data to be collected, duration of followup, recruitment targets, and expected loss to followup. If the document “PMCF plan for SCS-PNS Therapy (NDHF1463-185081)” has already been updated to include the subject device (noting that the CER refers to inclusion in this document in future tense), then please also provide this, to contribute to the assessment of compliance with EP 1, 3, 4, 6 and 14.

Sign-Off – Medical Advisor

Name	s.22		
Signature	Signed electronically in TRIM	Date	15 March 2024

Senior Medical Advisor's comments

Sign-Off – Senior Medical Advisor

Name	s.22		
Signature	Signed electronically in TRIM	Date	15 March 2024

Clinical review Round 2

Information provided in response to questions from previous round of assessment	D24-1432239 Reply by manufacturer to R2 Clinical request for information.

Comments

The following responses have been received from the sponsor:

Question From Round 1	Sponsor Response	Reviewer Comments
1. A full study report of the ECHO-MAC study, to contribute to the assessment of compliance with EP 3, 6 and 14. a. Please explicitly state whether patient pain (via any validated instrument, NRS, VAS, etc) was measured	The purpose of the ECHO MAC study was to evaluate the performance of the Neuro Sense feature, hence, Medtronic did not collect any pain outcomes as a part of the ECHO MAC Study. The Neuro Sense feature is intended to reduce overstimulation by making adjustments to the stimulation amplitude, by comparing the measured ECAP amplitude to patient specific thresholds. As such, the feature is not intended to provide pain relief beyond what the therapy waveform does. Hence, the study focused on evaluating the performance of the Neuro Sense feature in reducing overstimulation with hypothesis driven endpoints and a randomized cross-over design, with the Neuro Sense off setting as the control arm. Long-term reduction in	The response confirms that the primary measure of effectiveness of the device (pain relief) was not collected. The change to closed loop therapy is a substantive change directly impacting the mechanism by which the device achieves its purported benefit. The applicant's response that the new method "is not intended to provide pain relief beyond what the therapy waveform" is noted, however does not address the need to prove that it is non-inferior.

	chronic pain is addressed in our response to Question #2, below. A copy of the ECHO MAC Study Final Report is provided as Attachment 1.01	
2. The claim of equivalence between the subject device and Intellis system is not currently sufficiently supported. Noting that the move to closed-loop stimulation is a substantive change in the therapy delivered, please indicate whether the applicant holds evidence of non-inferior performance, the follow-up duration of such data, and please submit any such data, to contribute to the assessment of compliance with EP 14.	Extensive response provided, see pages 3 – 5 of the applicant's response document (and associated appendices)	This response continues to assert substantial equivalence, and references a number of detailed documents. It is noted that in the attached equivalence assessment (NDHF1588-208318) the equivalence of the two systems with regards to change to closed loop stimulation is accepted only on the basis of evidence of non-inferiority of performance: "Where the Pain RC system differs from the Intelllis system, including the addition of ECAPS sensing, automated DTM programming, and other changes specified in Section 1.1, evidence is provided to demonstrate the difference does not affect device safety and performance." No acceptable evidence of non-inferior performance has been provided to date. (see response to question 1 above and response to question 4 below)
3. Please indicate whether the pain improvement threshold (from Farrar et al) was selected as a result of a formal selection process. Provide a justification for the selection of this source in selecting from the many available MCIC/MCIDs in the literature, to contribute to the	A minimum clinically relevant improvement on these pain scales has been defined by Farrar et al1. (**Attachment 3.01**), as a change in pain intensity of -1.7 points (-17 points on 100-point scale) or a 28% improvement from baseline. Farrar et al determined the minimum clinically important difference (MCID) based on a study of nearly 3,000 patients from 10 placebo-controlled pain studies (pharmacological), which utilized anchor-based determination of clinically meaningful change using Patient Global Impression of Change (PGIC) as a measure of patient reported improvement. A -1.7 point change in pain intensity correlated with PGIC categories of "much improved" or better. The CER pain improvement	The response is noted. The assessor is familiar with the papers cited. The assessor is aware that Farrar et al was developed exclusively in pharmaceutical interventions and specifically cautions readers about using the calculated cutoffs in studies longer than 12 weeks. In general terms it is for the manufacturer and/or sponsor to select the degree of pain improvement they wish to claim. However, the selection of a more modest threshold rather than the more substantial (and widely used) fifty percent reduction will mean that establishing compliance with EP 6 is

assessment of compliance with EP 6 and 14.	threshold from Farrar et al was selected due to the broad focus on chronic pain, the variety of studies, the large number of subjects, and the similarity between the subject's indications and SCS patients. Farrar et al is a well-known and frequently cited publication that established an MCID for chronic pain interventions. For example, the MCID threshold from Farrar et al was adopted by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) consensus committee to provide recommendations for interpreting clinical importance of treatment outcomes in clinical trials of the efficacy and effectiveness of chronic pain treatments (Dworkin et al2, **Attachment 3.02**). The IMMPACT consensus statement suggested that reductions of ≥30% or at least a -2 point (-20 on a 100-point scale) change reflect a moderate clinically important difference. The same group has also published guidelines for best practices to be adopted for the design of clinical trials evaluating therapies for chronic pain.	dependent on demonstrating a more safe intervention with only minor risks or that significant risks are rare.
4. Please indicate whether any interim analyses of the Neuro Sense study described in section 7.2 of the CER are available, to contribute to the assessment of compliance with EP 14	The Closed-Loop Australia 3- month Report is provided as **Attachment 2.02** The following observations were made from the 3-month study results: □ Reduction in overstimulation and significant pain relief (86% reporting ≥50% at 3 months) demonstrate Inceptiv's effectiveness in managing chronic pain, as required by EP 14. □ The study demonstrated an absence of unanticipated adverse events and similar rates compared to other SCS studies. □ Improvements in health-related quality of life reported by participants further support the positive impact of Inceptiv on patient well-being, a relevant factor for risk-benefit assessment in EP 14. The 3-month study data demonstrate both effectiveness in pain reduction and a favourable safety	The study report has been reviewed. It is noted that the sponsor has specifically indicated they do not intend to include a minimum baseline pain score in the intended use of this device. The inclusion of a minimum pain score in this study is therefore a substantial difficulty, as this patient group is therefore meaningfully narrower than the intended clinical use population. Other exclusion criteria include high levels of opioid painkiller use, mental health history, any injury claim, as well as *recommendations* not to enrol patients with particular pain syndromes, all of whom would be eligible for treatment in clinical

	profile for Inceptiv closed-loop SCS therapy. Longer-term follow-up data from the CL study will be incorporated into clinical evaluation activities as data become available.	practice under the proposed intended use. Single arm results in a small very highly selected cohort (especially when excluding a large number of patients eligible for therapy under the proposed intended purpose) will not be able to provide evidence that is sufficiently generalisable to support device inclusion. In this cohort of 75 patients, 32 adverse events were recorded by the three month follow-up visit of which 16 were serious. 7 of the 16 serious events were device related (in 7 patients).
5. For the patients in table 54 of the CER, to contribute to the assessment of compliance with EP 3, 6 and 14: a. Please indicate how many of the 215 patients with 12 month change scores for general pain i. Improved by 50% or more ii. Improved by 80% or more b. Please indicate how many of the 170 patients with 12 month change scores for back pain i. Improved by 50% or more ii. Improved by 80% or more c. Please indicate how many of the 151 patients with 12 month change scores for leg pain i. Improved by 50% or more	Extensive response provided, see pages 6-8 of (and associated appendices) The requested table is: Table 1: Responder Rates [a] at 12-Month Follow-Up s.47	The applicant asserts this is “a large, representative international population”. The applicant asserts that results seen in clinical trials may not match those seen in “real world” settings due to restrictive selection criteria, the evaluator agrees. The answer states that “These real-world data sets, often collected in registries (such as Medtronic’s PSR), complement RCTs by enrolling a more representative patient population.” The evaluator agrees. The answer warns against over-interpreting the “general” pain score noting that “Additionally, the generalized pain score considers pain throughout the body, beyond the back and/or limbs targeted by the SCS system. Since the general pain rating can be influenced by changes in pain unrelated to the targeted area, these general measures can be less reflective of the impact of SCS Therapy”. This seems a reasonable argument.

12-Month Score Type	≥ 50% Pain Reduction n/N (%)[a]	≥ 80% Pain Reduction n/N (%)[a]
General Pain	(23.2%)	(7.1%)
Back Pain	(27.8%)	(11.8%)
Leg Pain	(37.3%)	(17.6%)

ii. Improved by 80% or more		It is noted that the applicant uses cutoffs of 50% and 80% in promotional and educational material relating to the predicate device. The results provided unarguably differ markedly from the results the manufacturer chooses to publish and promote. An absolute minority of patients met the definition of “responder” in a population the sponsor describes as “representative” of clinical practice. 28% of patients met the definition of responder for back pain and 37% for leg pain. See response for question 6 below for further context.
6. Please indicate whether the applicant plans to publish the results in table 54 of the CER (containing the PSR change in pain results), or if not, whether the applicant plans to communicate the same to patients and prescribers, to contribute to the assessment of compliance with EP 13.	While Table 54 of the CER shows data collected across various conditions and times, a combined analysis of these data have not been published to date and Medtronic does not have current plans to publish this type of combined analysis to patients and prescribers. However, cohort specific analysis has been presented in the form of scientific abstracts at conferences related to Pain Management (e.g., DPN, MRI). Medtronic publishes scientific abstracts and manuscripts to a publicly accessible webpage: https://www.medtronic.com/us-en/healthcare-professionals/therapies-procedures/neurological/spinalcord-stimulation/clinical-outcomes/publications.html. Copies of the above-mentioned abstracts are also included in this response as: □ Attachment 6.01 – Calodney et al., 2022, ASRA PSR Intellis Abstract □ Attachment 6.02 – Calodney et al., 2023 ASPN PSR Impedance Abstract □ Attachment 6.03 – Hatheway et al., 2024. SCS for PDPN: Consistent Outcomes from Multiple Studies □ Attachment 6.04 – Mohabbati et al. 2024 NANS CL Australia 3M Poster	It is surprising that the combined analysis referred to by the applicant (i.e. the performance data in the row above this one) have not been published. The sponsor describes a situation in which, for the predicate device which is currently supplied in Australia: • The sponsor holds substantial data on the pain relief achieved by these devices in a setting they describe as “real world” in a population they describe as “representative” • The results are substantially worse than is publicly claimed for the device • The sponsor indicates they have not informed prescribers or patients and have no plans to do so. This is a very concerning situation.

7. In table 66 of the CER, the author has extracted pain change scores from the PSR in the subgroup with more severe baseline pain (table 56), rather than all on-label usage. Please indicate whether the applicant is seeking to include a minimum score in the proposed indication, to contribute to the assessment of compliance with EP 3 and 14.	Medtronic does not intend to include a minimum score in the proposed indication. The sub-analysis of those with pain score of ≥5 was provided to remain consistent with the other prospective, interventional, randomized-controlled studies summarized in Tables 55-56 and Table 66 that use this eligibility criterion for participation in the study. The larger baseline pain score allows for an adequate effect size of the treatment (and control) being evaluated in the study without a floor effect. Tables 53-54 provide the pooled performance data without the ≥5 baseline pain criterion being applied.	The response is noted. It is noted that this approach does not align with the very restrictive criteria in the Neuro Sense study.
8. The data in support of adding diabetic peripheral neuropathy falls well short of what is required, please indicate if the applicant would like to submit any further data in support of this indication, to contribute to the assessment of compliance with EP 14.	Extensive response provided, see pages 9-12 of response document.	It is noted that just 16 patients have pain score changes in diabetic peripheral neuropathy at 6 months in the PSR registry using the claimed substantially equivalent device. This is not sufficient to support approval. The applicant also submits an overview of the published clinical literature. This does not identify any data from the subject or claimed substantially equivalent device. While performance in comparable devices can provide useful benchmarks for what constitutes state of the art performance, it cannot be used as indirect evidence in the absence of a substantial equivalence claim.
9. Document NDHF1555-159439 refers to a product issue assessment for delayed spinal cord compression. Please indicate	Medtronic's customer complaint handling process identified a report of delayed spinal cord compression in an SCS patient as a potential safety concern. This led to the creation of the product issue assessment	This answer is noted, and will be considered in the overall context of device safety and EP 6.

whether this arose from a safety signal or was a theoretical risk identified on routine review, to contribute to the assessment of compliance with EP 1, 2, and 4.	referenced in NDHF1555-159439, which reviewed published medical literature and product event reports. The reviewed evidence suggests that in some patients, delayed spinal cord compression may occur due to the formation of reactive fibrous tissue, sometimes with an inflammatory component, with time to onset ranging from weeks to 20 years. The Information for Prescribers manual was updated to include delayed spinal cord compression as a potential adverse event as a direct result of this specific post-market monitoring activity. Below is an excerpt of page 14 of the Medtronic Pain Therapy Information for Prescribers manual (Attachment 9.01).	
10. Table 82 describes a very high rate of “non-serious” complaints. Please indicate whether loss of device function was a criterion for determining seriousness and reasonable to assume that none of the complaints in this table results in a loss of device efficacy, to contribute to the assessment of compliance with EP 1, 2, 3 and 4.	Medtronic considers a complaint reportable [serious] when the device has malfunctioned and the device or a similar device marketed by the manufacturer or importer would be likely to cause or contribute to a death or serious deterioration in the state of health of a person if the malfunction were to recur. This includes (but is not limited to) malfunctions leading to a loss of device efficacy, so long as they would be likely to cause or contribute to a death or serious deterioration in the state of health if the malfunction were to recur. None of the complaints in Table 82 resulted in or had a history of malfunction that would be likely to cause or contribute to a death or serious deterioration in the state of health if the malfunction were to recur.	This answer provides clarity that “non-serious” complaints can include loss of device performance if they do not cause “death or serious deterioration in the state of health”.

11. The attached "implant manual" does not contain any information about adverse events, please indicate if a separate IFU document contains these and submit the same, or a modified version of the existing documents, to contribute to the assessment of compliance with EP 13A.	The structure of Medtronic's clinician manuals allows for the adverse events to be listed in the Information for Prescriber's (IFP) manual. The included adverse events are inclusive of potential AEs during implant and then throughout the patients' experience with SCS therapy. The proposed IFP is provided in Attachment 9.01.	The list of adverse events is included in this document and is found in the attachments on page 353 of the response. The manuals (when taken together) comply with the requirements of EP 13.
12. Information provided on the proposed PMCF is not sufficiently detailed. Please provide details including the outcomes of interest, the baseline demographic data to be collected, duration of follow up, recruitment targets, and expected loss to follow up. If the document "PMCF plan for SCS-PNS Therapy (NDHF1463-185081)" has already been updated to include the subject device (noting that the CER refers to inclusion in this document in future tense), then please also provide this, to contribute to the assessment of compliance with	Extensive answer provided, see pages 14 and 15 of the sponsor's response document.	The applicant's response is noted. This confirms a number of key points when considering the adequacy of the PMCF plan: - Patients will be enrolled in the PSR with similar data collection to previous generations of devices - Both device survival and efficacy measures will be recorded - 300 enrolments are targeted.

EP 1, 3, 4, 6 and 14		

The applicant has provided the requested data in appropriate formats and the responses are generally presented in a clear and logical manner.

As previously stated, this device is a closed-loop spinal cord stimulator for pain relief. It claims substantial equivalence to a predicate which did not have a closed loop design. This is an important and substantial change, noting that it is a direct change to the electrical stimulation delivery, the mechanism by which the device has its effect. As such direct evidence of clinical non-inferiority is required. The applicant has performed a randomized controlled trial (ECHO-MAC) but did not collect pain outcomes. The applicant did undertake a single arm study (see answer 4 above) however this fell short of establishing non-inferiority as the selection criteria (and selection recommendations) for the population included was restrictive, and so did not capture the range of patients who would be eligible for this treatment in clinical practice under the applicant's proposed indication. The study also did not meet the TGAs published expectations for level of evidence or minimum duration (3 months).

For this reason, substantial equivalence has not been established. The submitted single arm study when considered on its own falls well short of the published expectations of the TGA for clinical evidence for implantable pulse generators, reporting outcomes only to three month and with no comparator. As such, EP 14 is not met.

Even if these issues were put aside, it would be unreasonable to accept this study as evidence unless the very restrictive inclusion criteria (minimum pain thresholds, excluding patients with mental health conditions, excluding patients taking significant opioids, excluding all the listed pain conditions) were reflected in the proposed intended purpose and published contraindications.

The data submitted describing the performance of the predicate device is very concerning, especially considering the device is currently available on the Australian Register of Therapeutic Goods. 23% of participants met the minimum definition of responder (using the 50% definition from Medtronic's publications, trial registration, and published material) on "general pain", 28% for "back pain", and 37% for "leg pain". The response provided (page 7 of the 41JA response) cautions against over-interpreting the "general pain" outcome as this will likely capture pain "in many other areas of the body" which spinal cord stimulation would not be expected to treat. This seems reasonable. Despite this the remaining results remain concerning and demonstrate that most patients do not receive the minimum level of pain relief to meet the manufacturer's publicly used definition of responder, when used in clinical practice, in a population the sponsor describes as "representative". This is substantial evidence that the subject device does not comply with EP3, and that the predicate device clearly does not comply with EP3. This also means that, for the predicate Intellis device:

- The sponsor holds substantial data on the pain relief achieved by these devices in a setting they describe as "real world" in a population they describe as "representative".
- The results are substantially worse than is publicly claimed for the device by the manufacturer
- The sponsor indicates they have not informed prescribers or patients and have no plans to do so.

It is impossible to see how patients can give meaningful informed consent in this setting, nor how prescribers can make reasonable recommendations about care.

The sponsor now asserts that the proper threshold for judging pain relief from the Intellis device is an improvement of 1.7 points (out of 10) or more. This is derived from Farrar et al. This is not reasonable. Firstly, Farrar et al examined purely pharmaceutical interventions. Secondly, it was limited to studies of 12 weeks duration or less. Thirdly, the conditions treated in Farrar bore little

relation to those in which the Intellis device is indicated (see table 1 of Farrar et al) with three of the ten included studies for postherpetic neuralgia.

Even putting aside these limitations, were 1.7 points reduction considered a reasonable minimally clinically important difference, establishing that this is achievable would not establish compliance with EP 6 unless the side effects were at least as minimal. This does not appear to be the case. The rate of complications is very concerning. As per the round 1 assessment adverse events are common, occurring in 40% of patients in the first year of the VECTORS study and 11% in the PSR register. The risk management report describes catastrophic risks occurring occasionally and critical risks occurring frequently as inherent risks relating to the implant procedure. This response from the sponsor contains data from the subject device indicating that 16/75 patients had an adverse event that was deemed device related by three months, and that 7/75 had a serious adverse event that was deemed device related by three months. Considering the very high rate of adverse events, across multiple data sources, a claimed difference in pain of 1.7 points out of 10 is not sufficient to demonstrate compliance with EP6.

The previous concerns about EP 13 have now been addressed, with the provision of additional documentation from the sponsor.

There were no issues identified which required ACMD advice, from a clinical perspective.

Clinical assessor's conclusion:

The sponsor's responses do not establish compliance with the essential principles for the following reasons.

Compliance with EP 14 is not established due to a lack of clinical evidence. The change to closed loop stimulation is considered significant, because it is a change to the actual electrical stimulation delivered, which is the mechanism by which the device achieves its effect. While the manufacturer did conduct a head to head order randomised controlled (crossover) trial examining their intended reduction in side effects, this trial collected no pain outcomes of any kind meaning it cannot establish non-inferiority of performance. The sponsor did submit some direct clinical evidence for the subject device, however it fell well short of the TGA's published expectations for devices of this kind in the Clinical Evidence Guidelines, being (clearly) less than 12 months duration, and (more arguably) not the highest practical level of evidence. This study also features restrictive inclusion criteria which are not reflective of the proposed intended purpose or device documentation.

Because of the lack of clinical evidence, compliance with EPs 3 and 6 cannot be established.

Had substantial equivalence been accepted, compliance with EP 3 and 6 would not have been accepted given the very poor performance of the Intellis device in the manufacturer's post market surveillance registry, in which the majority of patients failed to experience the minimum level of pain improvement to be classified as "responders" (50%) under the most common definition, and the one that the sponsor uses in clinical trials. The sponsor asserts that an alternate definition of 1.7 points improvement on an 11 point scale could be used, however this benefit (MCID) is too small to establish compliance with EP 6 given the substantial side effect profile of these devices.

A substantial issue arises in that the sponsor has disclosed that the Intellis device has a response rate (50% improvement or more) of just 28-37% for most approved indications. This is substantially worse than published data on this device indicates. The sponsor confirms that they do not intend to inform patients or prescribers of this fact. Advice will be sought from the relevant sections as to what action should be taken (if any) in relation to this issue.

Clinical assessor's recommendation:

Based on assessment of the information provided for this application audit, the Inceptiv Spinal Cord Stimulation System does not comply with essential principles 3, 6 or 14 from a clinical perspective.

The sponsor's responses do not establish compliance with the essential principles for the following reasons.

Compliance with EP 14 is not established due to a lack of clinical evidence. The change to closed loop stimulation is considered significant, because it is a change to the actual electrical stimulation delivered, which is the mechanism by which the device achieves its effect. While the manufacturer did conduct a head to head order randomised controlled (crossover) trial examining their intended reduction in side effects, this trial collected no pain outcomes of any kind meaning it cannot establish non-inferiority of performance. The sponsor did submit some direct clinical evidence for the subject device, however it fell well short of the TGA's published expectations for devices of this kind in the Clinical Evidence Guidelines, being (clearly) less than 12 months duration, and (more arguably) not the highest practical level of evidence. Because of this lack of clinical evidence, compliance with EPs 3 and 6 cannot be established.

Had substantial equivalence been accepted, compliance with EP 3 and 6 would not have been accepted given the very poor performance of the Intellis device in the manufacturer's post market surveillance registry, in which the majority of patients failed to experience the minimum level of pain improvement to be classified as "responders" (50%) under the most common definition, and the one that the sponsor uses in clinical trials. The sponsor asserts that an alternate definition of 1.7 points improvement on an 11 point scale could be used, however this benefit is too small to establish compliance with EP 6

Sign-Off – Acting Senior Medical Advisor

Name	s.22		
Signature	Signed electronically in TRIM	Date	9 May 2024

Senior Medical Advisor's comments

Sign-Off – Senior Medical Advisor

Name	s.22		
Signature	Signed electronically in TRIM	Date	9 May 2024

Version history

Version	TRIM Reference	Description of change	Author/s	Effective date
V1.0	D20-3667497	New FORM	s.22	13 Jan 2021

Appendix 1 – Documentation provided by the sponsor

To be completed by Clinical Section Reviewer

Type of documentation	Document name, version number/reference & date	TRIM location
Labels		
IFU		
Patient information leaflet (PIL)		
Patient information card (PIC)		
Advertising		
Clinical evaluation report (CER)		
CV of clinical expert		
Risk management report		
FMEA		
MRI information		
(Other documents)		