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MASTERS-D 2

Clinical Investigation Plan

Version 4.0

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P15-01

Global Sponsor
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Change History record

CIP Change History		
Version	**Summary of Changes**	**Author**
1.0	Initial Release	[redacted]
2.0	• Section Approval Sheet: Will be kept separately • Section CIP SYNOPSIS: CIP synopsis has been incorporated to the CIP. • Section: A.2.3 Cages Systems: The AVILA™ Interbody Fusion Device has been added • Sections B.1.2. Primary objective and endpoint AND B.1.3. Secondary objectives and endpoints (both in main CIP and in Synopsis); B.4 Study hypothesis; B.7 Sample size; and throughout the document: Clarification that the population is Degenerative Disc Disease (DDD) patients. As it is mentioned in the inclusion criteria already. • B.1.2 Primary objective and endpoint: Definition of "procedure" clarified: "In this prospective study design, patients will be enrolled in one of the 6 procedure groups: ALIF, OLIF, DLIF, PLIF, TLIF or MIDLF" • Section Rationale for selection of the secondary endpoints – Fusion: ○ Clarification that "If no fusion is observed during the first fusion assessment further fusion assessment(s) will be at the discretion of the investigator". ○ Modification of fusion success definition: "If a subject shows fusion success at early timepoints and non-fusion at a later timepoint, the fusion status at all earlier points should be considered as non-fusion." • Section Rationale for selection of the secondary endpoints - second surgery: ○ Terminology harmonization: intervention replaced by surgery. ○ Clarification in the paragraph that the second surgery will be collected as well for "adjacent level(s)" as already mentioned in the title. ○ Removal of "reoperation form" as not existing in the case report form. • Section Rationale for selection of the secondary endpoints DN4 questionnaire, (Douleur Neuropathique 4 (neuropathic pain)): ○ Full paragraph added to explain the DN4 questionnaire as well as rational and references • Section Additional spinal cord stimulation or pain pump: Addition of this section as additional measurement • Section B.3 Definitions Study Procedures: L4-L5 added in ALIF definition as these levels can also be treated with an ALIF procedure • Section B.5 Study design: The terminologies "Cohort", "Pragmatic" and "patient centered case series" were removed in order to align with other sections. • Sections B.6 Randomization and blinding; B.7.Sample Size; E.1. Screening; E.11. Study deviations and CIP changes: Removal of the terminology "cohort" to align with other sections. • Section B.7 Sample size: Clarification added that "The amount of patients with spondylolisthesis versus non-spondylolisthesis will be monitored during the study. […]"	[redacted]

	this will allow to make sure that the sample size defined in this protocol is reached in case high amount of non-spondylolisthesis versus spondylolisthesis patients are enrolled.
	• Sections B.7 Sample size AND E.9 Adverse events: References to Canada are removed as this country will not participate
	• Sections B.7 Sample size:
	  ○ Correction of terminology "cohort" and replacement by "procedure": "A minimum enrollment of 80 patients in each procedure (ALIF, OLIF, DLIF, PLIF, TLIF or MIDLF) is required."
	  ○ Addition of information on site/region enrollment limit
	  ○ Latin America and Middle-Est Overview of patient enrollment has been increased to a maximum of 20 enrollment per site and 15 per procedure
	• Section(s) B.8 Number of investigation sites and study duration AND Synopsis - Patient Population:
	  ○ Timelines adaptation: Patients "will be enrolled over a period of around 28"; The total duration of the study will be of approximately 88 months; Enrolment will start in 2016 and the final follow up visit is expected in 2023.
	  ○ Addition of "Depending on enrolment progress, study timelines are subject to change."
	• Section C SUBJECT SELECTION:
	  ○ **Inclusion Criteria:**
	  ○ Inclusion of patient who are 18 years old by changing to more or equal: "Patient is ≥ 18 years of age"
	  ○ Clarification that: "For a double level instrumented fusion, the same procedure must be used for both levels"
	  ○ **Exclusion Criteria:**
	  ○ Clarification that patient participating to a concurrent clinical study should not be enrolled if "that may confound study results"
	• Section D.2.1EC/IRB approval: Clarification that "when the sponsor is responsible for EC submission, a written documentation from the sponsor is required. "
	• Section D.2.3 Revisions in Patient Information and Informed Consent Form: Clarification that "in case the revised Informed Consent has no impact on previously enrolled patients, the Informed Consent won't need to be re-signed by already enrolled patients."
	• Section D.3 Regulatory compliance: Addition of "If any action is taken by a EC/IRB with respect to the investigation, the information will be forwarded to the sponsor."
	• Table 2: Description of Procedures and Assessments at different time intervals:
	  ○ Addition of "DN4 for back and DN4 for leg" at Baseline, 3m, 1 year
	  ○ Addition of "As DN4 questionnaire has been added in the CIP amendment 2.0, the patients who were enrolled under CIP version 1.0 will NOT complete the DN4 retrospectively but will complete the DN4 questionnaires for any upcoming follow up visits."
	• Section E.1 Screening: Clarification of Subject Identification & Enrollment Log maintenance
	• Section E.3 Baseline procedures: Addition of "The identification of neuropathic pain will be assessed by the DN4 questionnaire in the back and in the leg."
	• Section E.4 Implant or procedure aspects: Clarification "Patient […] might not be operated to treat the degenerative lumbar spine or might have a different procedure for other reasons"
	• Section E.6 Follow up requirements: Addition of "The identification of neuropathic pain will be assessed by the DN4 questionnaire in the back and in the leg at 3 and 12 months follow up."	

	• Sections E.7 Data collection requirements AND F.1.2. Data collection: Correction: patient satisfaction removed (not collected in this study)
	• Table 3: Summary of scheduled procedures and assessments AND Synopsis Table 1: Summary of scheduled procedures and assessments: Addition of DN4 in the back and DN4 in the leg at Baseline, 3 months and 1 year
	• Section E.8 Source documents: Addition of "DN4 in the back and DN4 in the leg"
	• Section E.9.1.1 Definition/classification - Related to the disease: Definitions changed in order to be aligned with MEDDEV 2.7/3 definitions
	• Section E.9.1.2 Recording and reporting of Adverse Events: Clarification of the reporting
	• Section E.9.1.3 Recording and reporting of Device Deficiencies: Clarification of the reporting
	• Section E.9.1.5 Reporting of product complaints: This section has been reworded entirely to be clearer for the site
	• Section E.9.3 AE/DD reporting in case eCRF cannot be accessed and/or emergency contact details:
	  ○ Section has been added to clarify the actions needed in case CRF not accessible.
	  ○ Emergency contact details updated
	• Section E.10 Subject accountability:
	  ○ Addition of "Patient did not undergo the instrumented lumbar fusion as defined in this protocol"
	  ○ Addition of "Subjects withdrawn from the study will only be replaced when patients did not undergo the instrumented lumbar interbody fusion with posterior fixation as defined in this protocol if the enrollment is still open. In that case only, these patients will not contribute to the site and region specific enrollment limits nor to the maximum amount of patient enrollments per procedure."
	• Section E.11 Study deviations and CIP changes AND Table 6 Deviation - Actions overview table: Addition of deviations that will be tracked in the eCRF
	• Section F.1.4 Data review and processing: Clarification of the Data electronic storage maintenanceSection F.2.2 Interim Monitoring visits: the percentage of data monitored is replaced by level of monitoring for correctness.
	• Section G.1 Analysis of clinical data: Clarification of Analysis data set
	• Section G.1.2 Analysis of Secondary Endpoints:
	  ○ Change in Fusion analysis: "Time-to-event-analysis will be conducted for fusion success"
	  ○ Addition of DN4 analysis
	• Section G.2 Publication Policy: Addition of ClinicalTrials.Gov reference
	• Throughout the documents: Duplications and typos have been respectively deleted and corrected. Furthermore the abbreviations were harmonized
	• Section REFERENCES: This section has been updated
	• Section K APPENDICES: Clarification that List of sponsor staff and List of Advisory Committee Members will be kept separately	

3.0	• Minor textual changes throughout the Clinical Investigation Plan • Incorporated all requirements of CIP Region Specific Addendum: Asia Pacific Version 2.0, 25 Oct 2016 in this Masters-D2 CIP version 3.0. • Section title page: added local sponsors for China (new address), Korea and Latin America • Section CIP SYNOPSIS: ○ Timelines have been adjusted to reflect the current estimated timelines.	[redacted]

	○ Inclusion criteria: Reference to section Medical Devices has been corrected to refer to section Device information. ○ Clarified that Medtronic BRC is the Global Sponsor • B.1.2 Primary objective and endpoint: Moved primary endpoint after objective to have a more logical order. Removed duplicate text in section rationale for primary endpoint selection. • B.5 Study design: ○ An email will be sent to the participating sites to inform the investigators (not the patients as initially indicated) when the enrollment for a specific procedure is complete. ○ Refusal of study participation as well as enrollment into the study will be recorded ~~for statistical purposes from the investigators~~ on the screening log. This sentence was removed because no statistical analysis will be performed on the screening log. • B.6 Randomization and blinding: Moved ODI information to section B.5 which describes measures to avoid bias. Clarified that blinding is not applicable in this study. • B.7 Sample size: ○ Aligned regions with synopsis by removing specifications of individual countries ○ Restructured the section about enrollments. ○ Included information from Asia Pacific addendum with regard to enrollment limits. Adjusted enrollment max per procedure for Korea to 20. Included a potential additional site for China and Europe to align with the estimate of 38 sites. ○ Added : patient enrolment may be stopped when the required sample size for the primary endpoint has been reached. ○ Minimum enrolment of 80 patients in each procedure (ALIF, OLIF, DLIF, PLIF, TLIF or MIDLF) reduced to 40 and added sentence that study will aim to balance the subjects equally between the procedures. ○ Adjusted enrollment maximum per site for Europe to 40 patients and increased the enrollment maximum per procedure for each site in Europe, Latin America and Middle East. ○ Clarified that the limits in table 1 may be subject to change during the course of the study and will be communicated as appropriate to the investigators and EC/IRB, if required. ○ Added note to allow for change in enrollment limits per procedure to have a better distribution of procedures amongst the sites and regions. • B.8 Number of investigation sites and study duration: Timelines have been adjusted to reflect the current estimated timelines. • C.1 Inclusion and exclusion criteria: Inclusion criteria: Reference to section Medical Devices has been corrected to refer to section Device information. • D.2.2 Informed consent process: Clarified that “the process must be documented” before any clinical study related activity takes place. • D.2.4 Data Release Consent process: Clarified that “the process must be documented” prior to releasing any personal information of the patient.	

	• D.3 Regulatory compliance: Clarified that EC/IRB may also impose additional requirements. Removed reference to APAC CIP addendum since all requirements are captured in this version of the CIP. • D.4 Training requirements: Use of data collection tools (CRF training updated to EDC training for correctness) • E.7 Data Collection requirements: 4 weeks (± 2 weeks) visit changed from mandatory hospital visit to potential phone visit. • E.9 Adverse events: References to China safety and vigilance reporting requirements are added from the Asia Pacific Addendum. The Korea safety and vigilance reporting requirements are updated to reflect the new requirements. • E.9.1.1 Definition/classification: References added to Korea GCP and UADE definition included from Asia Pacific Addendum. • E.9.1.4: Adverse Event and Device Deficiency review process: Table 5 reporting requirements added for Korea. • E.9.1.5: Removed reporting of product complaints according to local Product Complaint Handling SOP as the investigators are not trained on Medtronic procedures so they wil only report via the regular channels for market-released products. • F.2.2 Interim Monitoring Visits: Updated source data verification language to align with the monitoring plan. Added certified copy definition. • G.1.4 Interim Analysis: Section updated to provide more clarification on the interim analysis. • H.4.1 Insurance: Replaced Medtronic Plc. With Medtronic after advice from legal.	
4.0	• B.7 Sample size Equivalence range was redefined from -7.5, 7.5 points to -10, 10 points ODI improvement at 3 months between anterolateral and posterior group Due to the change in equivalence range the estimated sample size per group (anterolateral procedures versus posterior procedures) was updated from 122 to 70. The estimated total sample size for spondylolisthesis patients with DDD was decreased from 244 to 140 As from the MASTERS-D study it is known that approximately 50% of the patients with degenerative disc disease have spondylolisthesis ≥ grade I. Hence the required total sample size was also changes from 244/0.5=488 to 140/0.5 = 280. The anticipated patients to be enrolled in the study was also changed from 560 to 350. Minimum enrollment of 40 patients was changed to 20 patients in order to accommodate also the lower sample size of the study. In Table 1: “Overview of patient enrollment limits in Europe, Latin America, Middle East and Asia Pacific per site and per procedure. “, the Middle East was removed as participating region and estimated number of sites corrected for EU and China.	[redacted]

	• B.8 Number of investigation sites and study duration: Number of estimated patients updated per section B.7 and Middle East was removed as participating region • G.1.1 Analysis of Primary Endpoint: Equivalence range update from (-7.5, 7.5) points to (-10, 10) • E.7. Data collection requirements - Table 1: Summary of scheduled procedures and assessments - lay out reformatted. • H.3.5 Record retention : added information for Europe in order to comply with EU MDR: The documentation shall be kept for a period of at least 15 years after the clinical investigation with the device in question has ended • General comment: This CIP amendment (Version 4.0) is related to an increase of equivalence range and the impact is that number of patients enrolled into the the study is reduced from about 560 to approximately 350 patients, Even though the number of patients enrolled in the study worldwide is mentioned in the Patient Informed Consent/Patient Data Release form it has been decided not to reconsent the patients unless if this is requested by the IRB/EC. Rationale for not reconsenting patients is the following: - The amendment does not include new information that might affect patients' health, welfare and willingness to continue participation in the study. - The amendment does not change assessments for the patients already included or to be included in this study. - It is not expected that a decrease in sample size will cause already enrolled patients to change their mind about study participation - In case new information becomes available from this or other studies that may affect the patient's health, welfare, or willingness to stay in this study, the patient's will be informed about it as soon as possible. For those sites were enrollments are still expected after approval of CIP version 4.0 a site specific consent will be created and submitted for approval to the ethics committee indicating the correct number of expected enrollments. Since the change is only related to the number of pts enrolled in this study, no new master template nor country specific templates will be prepared as no other changes will be made to the already previously approved PIC/DRF.	

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TABLE OVERVIEW

CIP SYNOPSIS

Name of Trial	MASTERS-D 2
Title of Trial	A Prospective, 5-Year, Global Study on MAST™ Minimally Invasive Fusion Procedures for the Treatment of the Degenerative Lumbar Spine.
Identification #	P15-01
Purpose	▪ To evaluate the effectiveness of MAST techniques for anterior/lateral and posterior approaches in patients with spondylolisthesis (≥ grade I). ▪ To assess how single or double level MAST fusion procedures PLIF, TLIF, DLIF, OLIF, ALIF, or MIDLF are used in surgical practice and to describe long-term safety and effectiveness in a broad patient population of patients with degenerative lumbar disc disease .
Design	Prospective, Global (multi center), Post Market Release (PMR) Study
Name of product	Medtronic CD Horizon® Spinal Systems. CD HORIZON® Spinal System consists of a variety of rods, hooks, screws, plates, and other connecting components used to build a spinal construct. Instrumentation is also available to facilitate implantation of these components.
Primary Objective & Endpoint	To demonstrate that Degenerative Disc Disease (DDD) patients operated for spondylolisthesis fare equally well regardless of the surgical procedure (anterolateral or posterior) performed as measured by the improvement of Oswestry Disability Index (ODI) at 3 months as compared to baseline. Endpoint: Improvement of disability at 3 months post-operatively as compared to baseline.
Secondary Objectives & Endpoints	▪ To evaluate whether DDD patients without spondylolisthesis fare equally well regardless of the surgical procedure (anterolateral or posterior) performed, as measured by Oswestry Disability Index (ODI) at 3 months ▪ To observe and document clinical and radiological outcomes through 5 year follow-up (except for ODI at 3 months) - Improvement of ODI as compared to baseline - Improvement of VAS back- and leg pain intensity as compared to baseline - Improvement of EQ-5D as compared to baseline - Neurological success - Fusion success - Secondary Surgeries at index and/or adjacent level(s) - Adverse Events ▪ To observe and document the patients' short term recovery after surgery - Time needed for first ambulation: Days needed for patient to get out of bed and ambulate with or without assistance - Surgery Recovery Day: Days after the surgery, fulfilling following criteria: ✓ No need for intravenous infusion of analgesic drugs ✓ No ongoing surgery related adverse events impeding discharge ✓ No need for nursing care ▪ To document health resources consumption and perform economic analyses. ▪ To observe and document the patient profile when choosing a particular minimally invasive fusion procedure.

Patient Population	Approximately 350 patients suffering from lumbar degenerative disc disease (DDD) will be enrolled over a period of around 4 years in approximately 30 sites located in Europe, Middle East, Latin America and Asia Pacific. As the patients will be followed during a period of 5 years after the surgical procedure, the total duration of the study will be of approximately 9 years. Enrollment has started in 2016 and the final follow up visit is expected in 2025.
Treatment	A single or double level instrumented fusion using minimally invasive PLIF, TLIF, MIDLF, DLIF, OLIF, ALIF procedures for the treatment of the degenerative lumbar spine. The use of a posterior fixation system is mandatory in this study and will be either mini-open and/or percutaneous.
Inclusion Criteria	▪ Patient is ≥ 18 years of age (or minimum age as required by local regulations) ▪ Patient has degenerative disc disease and an indication for a single or double level instrumented lumbar fusion for the treatment ▪ Patient agrees to participate in the study and is able to sign the Data Release Form/Informed Consent ▪ The procedure planned for the patient complies with the labeling of the Devices that may be used in the surgical procedure as described in the section Device information of this Clinical Investigation Plan ▪ Patient is planned to be submitted to a minimally invasive fusion procedure using a posterior (PLIF, TLIF, MIDLF) or anterolateral (OLIF, ALIF, DLIF) technique * ▪ The patient is willing and is able to perform study procedures and required follow-up visits. * For a double level instrumented fusion, the same procedure must be used for both levels.
Exclusion Criteria	▪ Patient that has already undergone a lumbar fusion surgery ▪ Patient that has already undergone open lumbar surgery other than standard decompression surgery ▪ Indications for the procedure other than degenerative spine disease like: Osteoporotic vertebral fractures, Spine trauma fractures or Spine tumor ▪ Illiterate or vulnerable patients (e.g. minors, participants incapable of judgment or participants under tutelage) ▪ Concurrent participation in another clinical study that may confound study results.
Clinical Procedures and Assessments	Assessments will be done pre-operative, during surgical procedure and hospital stay and post-operative at 1, 3 months, 1, 2, 3, 4 and 5 year follow up. See table 1 (below)
Global Sponsor	Medtronic Bakken Research Center (Maastricht, The Netherlands).

Table 1: Summary of scheduled procedures and assessments

	Baseline	Day of Surgery (D0) (2)	Hospital Stay and Discharge (3)			Follow up assessments						
			D2	SRD	DIS	4(±2)week	3(-1.5/+3)month	1 year (±6 months)	2 year (±6 months)	3 year (±6 months)	4 year (±6 months)	5 year (±6 months)
Data Release Form *OR* Informed Consent Form	**X** (1)											
Demographics	**X**											
Medical History	**X**											
Surgery Indication	**X**											
Pain medication	**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Imaging (X-Ray, MRI and/or CT Scan)	**X**											
VAS (4)	**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
ODI	**X**					**X**	**X**	**X**	**X**	**X**	**X**	**X**
EQ-5D	**X**					**X**	**X**	**X**	**X**	**X**	**X**	**X**
Neuropathic pain: DN4 in the back and DN4 in the leg	**X**						**X**	**X**				
Work status	**X**					**X**	**X**	**X**	**X**	**X**	**X**	**X**
Rehabilitation Program						**X**	**X**	**X**	**X**	**X**	**X**	**X**
Neurological status	**X**					**X**	**X**	**X**	**X**	**X**	**X**	**X**
X-Ray or CT Scan (5)								**X**	**(X)**	**(X)**	**(X)**	**(X)**
Sagittal Balance(6)	**(X)**					**(X)**	**(X)**	**(X)**	**(X)**	**(X)**	**(X)**	**(X)**
Surgery and hospital data		**X**	**X**	**X**	**X**							
Adverse Events	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**

(1) Patient Informed Consent must be obtained prior to performing any study specific procedure

(2) Day '0' (D0) is the day of the surgery, D1 is the first day after surgery, D2 the second and so on.

(3) **SRD** = Surgery Recovery Day; **DIS** = Day of Discharge

(4) VAS Intensity scores for Back and Leg pains.

(5) CT scan or X-Rays at 1 year follow up. If no fusion is observed at 1 year follow-up, it will be at the discretion of the investigator to follow up if fusion can be observed (only if standard of care at the site).

(6) Optional only if it is routine practice (standard of care) at the site

TITLE AND STUDY IDENTIFICATION NUMBER

Study identification number:	P15-01
Study name:	MASTERS-D 2
Study Title:	A Prospective, 5-Year Global Study on MAST™ Minimally Invasive Fusion Procedures for the Treatment of the Degenerative Lumbar Spine.

A GENERAL INFORMATION

A.1 Introduction

A.1.1 *Study Rationale*

The basic tenet of minimally invasive spine surgery (MIS) and MAST™- (Minimal Access Surgical Technologies) is to effectively treat patients with the most reliable technique while minimizing tissue trauma. The advantages of the minimally invasive techniques in patients with degenerative disc disorders are low morbidity, shorter hospitalization time, less blood loss, less muscle damage, less narcotic use, quicker entry to physical therapy and more rapid recovery and return to work/sports (1-3). However, it is generally considered that there is a need for monitored clinical studies with longer (5 years) follow-up (FU) due to the following aspects: 1) outcomes of MAST™ lumbar fusion techniques at long-term FU (> 2 years), in a larger patient population (> 300 patients) are still poorly documented; 2) there is an increased interest for cost-effectiveness data (4); 3) clinical and health economic benefits of the lumbar fusion may be apparent several years following the operation (5-7); FU beyond 2 years has been argued to be essential to formulate meaningful recommendations regarding the cost-effectiveness of lumbar fusion over non-fusion treatments (5); 4) FU for rare adverse events may require a longer (> 2 years) FU period (8). A Prospective, Long Term, Pragmatic Multicenter Post Market Release Study on MAST™ Fusion Procedures for the Treatment of the Degenerative Lumbar Spine (MASTERS-D, NCT01143324) was performed to observe and document standard of care surgical practice and to evaluate patient's outcomes up to 12 months FU. Spondylolisthesis (52.8%), stenosis (71.4%), and disc pathology (93.7%) were the most common preoperative degenerative lumbar pathologies. All surgeries were performed by experienced physicians. The majority of the patients were treated via a minimally invasive transforaminal lumbar interbody fusion (TLIF) approach, at one- (83%) and two-levels (17%), respectively (9). The results of the study on safety and effectiveness of MAST™ from 4 weeks up to 1-year FU showed low perioperative morbidity, early clinical recovery, improvements in Patient Reported Outcomes (PRO), high patient satisfaction and low complication rates.

The results of the initial MASTERS-D study generates a platform of interest for a new study including more MAST™ approaches for lumbar interbody fusion (LIF), and with a longer FU (up to 5 years): the MASTERS-D 2 study.

This new study aims to observe and understand the standard-of-care surgical practice, safety and effectiveness and evaluate patient's short and long-term outcome data, following a MAST™ single- or double level fusion procedure using a posterior lumbar interbody fusion (PLIF), transforaminal lumbar interbody fusion (TLIF), direct lateral lumbar interbody fusion (DLIF), oblique lumbar interbody fusion (OLIF), anterior lumbar interbody fusion (ALIF), or midline lumbar fusion (MIDLF) procedure in broad patient population of subjects with degenerative lumbar disc disease (DDD) with or without spondylolisthesis and/or stenosis. A lumbar interbody fusion in symptomatic patients can typically be performed by accessing the injured spine disc(s) either by an anterolateral (ALIF, OLIF, DLIF) or posterior (PLIF, TLIF, MIDLF) approach. The anterolateral procedures allow indirect decompression of the affected neural spinal structures while the posterior fusion procedures could allow direct decompressing (by tissue removal) of the neural spinal structures.

The results of the MASTERS-D 2 study are expected to contribute to better understanding of the different minimally invasive MAST™ procedures regarding patient pathology, surgical exposure and expected safety and clinical outcomes, from a short (intra- and peri-operative) to a long-term FU post-operatively, from the standard-of-care perspective.

A.1.2 *Costs/Health Economics*

The benefits of MIS techniques (smaller scars, diminished local pain, reduced blood loss, reduced post-operative wound pain, shorter hospital stay) were weighed against possible drawbacks, such as reduced orientation, steep learning curve, increased radiation exposure, dependency on technology, cost(10), and it was argued that comparative studies could convey a more realistic appreciation. However, the evidence concerning the economic value of the MIS surgery compared to open techniques is still scarce. Most of the data is provided by US studies, and concerns TLIF or PLIF surgical approaches.

Anderson *et al.* reviewed available literature, reporting outcome assessment and economic value for minimally invasive muscle-splitting and percutaneous surgical procedures, such as DLIF(XLIF), and ALIF(11). It was concluded that, regardless of the approach, parameters such as reduction in blood loss, surgical site infection, hospitalization costs, decreased pain, less soft tissue damage, decreased postoperative narcotics use, and quicker recovery all developed more favorable with MIS when compared with open procedures after two years.

Wang *et al.* performed a retrospective, nation wide, institutional data-base review of US data on 6106 (1667 MIS and 4439 open) inpatient hospital records from the Premier Perspective database (2002 to 2009), including patients who underwent a posterior lumbar fusion with interbody cage placement, to determine if minimally invasive interbody fusion is associated with cost savings when compared with open surgery (12). It was concluded that the majority of cost savings from MIS surgery were due to more rapid mobilization and discharge, as well as a reduction in outliers with extended hospitalizations. MIS lumbar interbody fusion also resulted in a statistically significant reduction in length of hospital stay and a reduction in total hospital costs with 2-level surgery after adjusting for significant covariates (age, sex, race, hospital geography and setting, payor, and comorbidities) (12).

Parker *et al.* found that MIS vs. open TLIF was associated with a decreased reported incidence of surgical site infection from 10 MIS TLIF cohorts (362 patients) and 20 open TLIF cohorts (1,133 patients), suggesting that MIS could be valuable in reducing hospital costs associated with spine care (13). MIS TLIF also resulted in reduced operative blood loss, shorter hospital stay and decreased 2-year cost, and accelerated return to work (14). Thus, MIS TLIF may represent a valuable and cost-saving advancement from a societal and hospital perspective.

Finally, a retrospective cohort comparison between MIS and open TLIF was performed to assess duration of narcotic use and return to work, long-term pain, disability, and quality of life (QOL) for MIS TLIF versus open TLIF (15). Both MIS and open TLIF provided long-term improvement in pain, disability, and QOL (EQ5D) in patients with back and leg pain from grade I degenerative spondylolisthesis. However, MIS TLIF allowed shorter hospital stay, reduced postoperative narcotic use, and accelerated return to work, reducing direct medical costs as well as indirect costs due to lost work productivity associated with TLIF procedures (15).

A.1.3 *Literature Update*

A literature review performed on December 11th, 2011 provided a comprehensive status of available relevant clinical evidence for minimally invasive spine fusion for degenerative diseases (data on file)(16). In total, a number of 971 patients were treated with minimally invasive surgical techniques for a 1-2 level fusion. Consistently through the assessed studies, the short-term advantages of MIS versus open surgery were confirmed, in terms of blood loss, time to ambulation, and hospital stay, while operation time and radiation exposure time could be higher. Yet, clinical outcomes, complication rates and fusion rates were similar. The MIS techniques allowed significantly lower infection rates compared to their open counterparts. It was concluded that further clinical and economic studies, were needed to provide additional information on the long-term clinical evidence for the MAST™ techniques(16).

A second literature update was performed at July 28th, 2014 by consulting the PUBMED database, for literature published after December 2011. The search generated 12 hits, of which four were retained for further analysis. Additionally, a search in the PUBMED database for articles specifically referring to the OLIF technique generated

three hits, of which one(17) reported only on pre-clinical data and was not further assessed. Several systematic reviews reporting on different MIS techniques were also considered for the literature update. Thus, a systematic review(3) was performed to determine whether MIS or open PLIF results in (1) better perioperative parameters, including blood loss, operative times, and length of hospital stay; (2) improved patient-reported outcome scores; (3) improved disc distraction; and (4) decreased frequency of reoperation and complications when compared with open PLIF procedures. It was concluded that MIS PLIF might lead to better perioperative parameters.

A meta-analysis based on 11 current randomized and non-randomized studies was undertaken by Zang *et al.* to assess MIS versus open TLIF(2). The pooled data on a total of 785 patients showed that MIS TLIF was associated with less blood loss, shorter hospital stay and a trend of better functional outcomes when compared with open TLIF. MIS TLIF significantly increased the intraoperative X-ray exposure. Both techniques had similar operative time, complication rate, and re-operation rate. A quantitative meta-analysis was conducted on published studies reporting fusion rates after open or MIS/mini-open single or multi-level TLIF procedures for the treatment of degenerative disease including stenosis with spondylolisthesis and degenerative disc disease(18). Twenty-three articles were identified which fit the inclusion criteria. In each of the 23 studies, TLIF was performed with pedicle fixation and fusion was evaluated using radiograph or computed tomography scan at minimum 6-month FU. Overall, the studies included 1,028 patients, of which 46.8% were female. The mean age of all patients was 49.7 years (range, 38-64.9 years), and the mean FU interval for assessment of fusion was 26.6 months (range, 6-46 months). The usage of recombinant bone morphologic protein was higher in the MIS TLIF group (50% vs. 12%). Mean fusion rate from 16 studies (716 patients) of open TLIF was 90.9%, whereas mean fusion rate from 8 studies (312 patients) of MIS TLIF was 94.8%. Complication rate was 12.6% and 7.5% for open and MIS TLIF, respectively. There were no controlled comparisons between open and MIS TLIF. It was concluded that the fusion rates for both open and MIS TLIF were relatively high and had similar ranges. Complication rates were also similar, with a trend towards MIS TLIF having a lower rate. The analysis provided clear benchmarks for fusion rates in open and MIS TLIF procedures for spine surgeons.

A retrospective study(19), including 179 patients receiving an OLIF procedure, performed at a single institution, with a FU time of 6 weeks-9 months discovered that the OLIF technique carried the same rate and risk for complications as the traditional anterior approach. It was concluded that OLIF can be performed easily and safely in lumbar spine from L2 to L5, and at L1-2 for selected cases, up three levels (via a “sliding window” through the abdominal muscles). Finally, the authors highlighted the need of a prospective study to compare the OLIF technique to the traditional anterior retroperitoneal approach.

A.1.4 *Risks-Benefits from a Literature perspective*

The primary objective of lumbar surgery in patients with spondylolisthesis and stenosis is to decompress the neural elements, as the patients will present symptoms such as neurogenic claudication, radiculopathy and/or low back pain(20). The available evidence contains generally a heterogeneous cohort of subjects, often combining patients with and without spondylolisthesis, treated by a variety of surgical techniques, limiting fusions to patients with instability(21). Lumbar fusion was considered appropriate to stabilize the spine in patients diagnosed with spondylolisthesis with stenosis, to avoid further misalignment, recurrence of pain and/or neurological complaints(22). For the stenosis patients that do not improve with conservative care, the role of fusion in the absence of degenerative processes was uncertain(21).

It was documented that the most common patient complications after decompression for lumbar spinal stenosis were per-operative dural lesions (23). The overall incidence for dural lesions was 7.4%, and high age, previous surgery and smoking were risk factors for sustaining a lesion. However, at 1 year FU the outcome was not affected negatively by these factors (23). Surgery for lumbar spinal stenosis in obese patients led to a clinically important (>10%) weight loss in 8% of the patients. The weight loss was not related to changes in patient-related outcomes (23). In the early 2000, the first reports were published on MIS TLIF with percutaneous pedicle screw fixation via tubular retractors, developed to avoid surgery-related lesions to the paraspinous muscle (20, 24, 25). It is well-documented and generally accepted that MIS techniques result in less blood loss, less post-operative pain, shorter hospital stay, faster recovery and fewer post-operative infections when compared with open techniques(13, 15, 26-32). A recent systematic literature review of 460 publications(33) was performed to examine the potential

complication of MIS and traditional surgery. A similar incidence of dural tears, infection, screw malpositioning, root injury and revision surgery rates was reported in both MIS and open surgery patients.

A systematic review of 258 publications regarding lateral fusion techniques (LLIF, XLIF(R), or DLIF)(34) examining the comparative safety and effectiveness for lateral techniques concluded that there was not sufficient evidence to compare the effectiveness of LLIF versus PLIF/TLIF surgery(34). However, the patients in the LLIF group experienced less estimated blood loss and a lower mortality risk compared with the PLIF group. No permanent neurological impairment, vascular or visceral injuries were observed in 97 consecutive patients from three different centers at a mean FU of 12 months(35). A rare complication of bowel perforation for XLIF in a 70-year old male was reported(36). ALIF open lumbar interbody fusion technique was associated with retrograde ejaculation (RE), demonstrating an increased risk (6.3%) in patients which received BMP-2 than in patients that were not exposed to BMP-2 (0.9%)(37). In fact, when using the rhBMP-2 in spinal fusion surgery a 10-50 times higher risk for AE than compared with sponsored peer-review publications(38) was communicated.

Concerns have been expressed about the instrumented fusion leading to a more stiff spine, and thus, to an increased risk for adjacent segment disease (ASD). ASD requires often re-operation, and is reported to be a common problem after lumbar spine fusion. However, there was no statistically significant difference of ASD incidence in patients undergoing open or percutaneous ALIF(8). Preoperative degenerative changes and post-operative sagittal imbalance were however important factors for developing ASD(39), along with high BMI(40) with a majority of the ASD re-operations being performed > 5 years post-surgery(41). A meta-analysis demonstrated that, when comparing with motion-preserving procedures, fusion patients were at higher risk of developing ASD(42). Within 10 years after surgery, it was predicted that 10% of patients would undergo additional surgery for ASD after index lumbar fusion, with PLIF (43, 44) and age > 60 years being risk factors.

Clinical outcomes after open spine fusion procedures in patients with degenerative conditions were reported to deteriorate continuously after 6 months post-surgery in a large cohort study with 6,376 patients, with approximately 18% having procedure-related complications, and 20% of these patients having a re-operation within 5 years. The complications occurred more frequent in patients having fusion than in patients having laminectomy or discectomy alone(45). Higher levels of back pain in 1,310 patients with DDD which had undergone an instrumented PLIF, at two years after surgery(46). However, the QoL was similar between the groups at 2 years post-surgery. MIS TLIF was comparable with open TLIF in terms of midterm clinical outcomes and fusion rates with the additional benefits of less initial postoperative pain, less blood loss, earlier rehabilitation, and shorter hospitalization, and a lower complication rate (47). There was no significant difference of ASD incidence in patients undergoing open versus percutaneous instrumented fusion following ALIF(8) or TLIF(48) procedures. It was suggested that MIS TLIF could be associated with decreased long-term morbidity compared with open fusion approaches(48), and had better results. In patients with degenerative spondylolisthesis MIS TLIF was equally effective as the conventional open TLIF procedure(47, 49-52), even though the quality of the available literature was questioned(53). MIS TLIF was a more cost-effective treatment than open TLIF for patients with degenerative spondylolisthesis and was equally effective as the conventional open TLIF procedure, although further financial analysis, including an analysis of indirect costs, is needed to better understand the full benefit of MIS TLIF (14, 53, 54).

A.2 Device information

The main set of devices that should be used in this study is the Medtronic CD Horizon® Spinal System. CD HORIZON® Spinal System consists of a variety of rods, hooks, screws, plates, and other connecting components used to build a spinal construct. Instrumentation is also available to facilitate implantation of these components. Additionally, other Medtronic family of ancillary devices, implants, instrumentation and bone grafts and substitutes (which are referred to as 'Devices') will also be used in the minimal invasive procedures within the scope of this study.

All Medtronic Devices to be used in this study, as listed below, shall be used within their intended use as described in the approved manual and Instructions for Use for which Medtronic obtained regulatory market release (e.g. CE Marking in Europe). Labeling of the devices will be in the appropriate local language. It is an investigator's responsibility to only use commercially available devices within intended use in the scope of this study.

In addition, any future approved similar devices or models may be used in the study.

A.2.1 *Posterior Fixation (Stabilization) Systems*

The CD HORIZON® Spinal System consists of a variety of shapes and sizes of rods, hooks and screws that has the function to help provide immobilization and stabilization of spinal segments as adjunct to fusion. The MAST™ platform provides generic instruments used to implant some of the CD Horizon® families of implants. The following systems are used for posterior stabilization of the treated spinal segments:

- *CD HORIZON® FENESTRATED Spinal System*
- *CD HORIZON® LONGITUDE™ Multi-Level Percutaneous Fixation System*
- *CD HORIZON® LONGITUDE™ II Multi-Level Percutaneous Fixation System 4.75*
- *CD HORIZON® LONGITUDE™ II Multi-Level Percutaneous Fixation System 5.5/6.0*
- *CD HORIZON® LEGACY™ 5.5 Spinal System (Solid and cannulated screws)*
- *CD HORIZON® SEXTANT® Rod Insertion System*
- *CD HORIZON® SEXTANT® II Rod Insertion System*
- *CD HORIZON® SEXTANT® II Spondylolisthesis Reduction System*
- *CD HORIZON® SOLERA® 4.75 Spinal System (Solid and cannulated screws)*
- *CD HORIZON® SOLERA® 5.5/6.0 Spinal System (Solid and cannulated screws)*
- *CD HORIZON® SOLERA® VOYAGER™*

A.2.2 *Access Systems*

The MAST™ (Minimal Access Spinal Technologies) platform incorporates instruments that allow the surgeon, in a minimally invasive approach, to reach the targeted lumbar anatomy by splitting the muscles with the insertion of a sequence of dilator tubes and reach the preferred tubular retractor diameter. This minimally invasive access allows a clear intraoperative visualization to perform the surgical procedure. The families of retractor systems, but not limited to, that may be used are:

- *ENDO-RING™ surgical retraction system*
- *MAST QUADRANT® Retractor System*
- *MAST QUADRANT™ Lateral Retractor System*
- *MAST™ MIDLF™ Retractor System*
- *METRx® II System*
- *METRx® X-tube® Retraction System*
- *51 Access System*
- *Other commercially available minimally invasive access systems*

A.2.3 *Cages Systems*

These are devices placed in the intervertebral space between two vertebrae to replace a disc and/or to restore disc height. These families of devices including the necessary instrumentation for their placement that may be used, but not limited to, are:

- *CAPSTONE® PEEK Spinal System*
- *CAPSTONE®TI Vertebral Body Spacer*
- *CAPSTONE PTC™ Spinal System*
- *CAPSTONE CONTROL™ Spinal System*
- *CRESCENT™ System*
- *CRESCENT® Spinal System Titanium*
- *CLYDESDALE™ Spinal System*
- *FUSE™ Spinal System*
- *I-FLY™ Threaded Fusion Device*
- *INTER FIX™ Threaded Fusion Device*
- *LOOP® Spinal System*
- *LT-CAGE® Lumbar Tapered Fusion Device*
- *SOVEREIGN™ Spinal System*
- *TELAMON® Vertebral Body Spacer*
- *VERTE-STACK® PERIMETER® PEEK Vertebral Body Spacer*
- *WAVE-D Spinal System®*
- *WAVE O Spinal System®*
- *AVILA™ Interbody Fusion Device*
- *Other commercially available cage systems*

A.2.4 *Plates*

Plates are devices used to obtain anterior stable, rigid segmental fixation. The family of devices including the necessary instrumentation for their placement that may be used, but not limited to, is:

- *PYRAMID™ Anterior Lumbar Plate*
- *Vantage™ Anterior Fixation System*
- *CD HORIZON® LEGACY™ Anterior Spinal System*
- *Other commercially available anterior plates*

A.2.5 *Bone Grafts and Substitutes*

Bone grafts and substitutes are used to promote bone formation which is necessary for a strong and successful fusion. The following, but not limited to, osteoconductive bone graft substitutes may be used:

- *BCP BiCalPhos® granules*
- *GRAFTON® Demineralized Bone Matrix*
- *InductOs®/ Infuse®*
- *MAGNIFUSE BONE GRAFTS*
- *MASTERGRAFT™*
- *Nanostim™ Synthetic Bone Paste*
- *Other commercially available bone grafts and substitutes*

B STUDY PLAN

B.1 Study Objectives and Clinical Endpoints

B.1.1 *Study Objectives*

The MASTERS-D 2 clinical study aims:

- To evaluate the effectiveness of MAST techniques for anterior/lateral and posterior approaches in patients with spondylolisthesis (≥ grade I).
- To assess how single or double level MAST fusion procedures PLIF, TLIF, DLIF, OLIF, ALIF, or MIDLF are used in surgical practice and to describe long-term safety and effectiveness in a broad patient population of patients with degenerative lumbar disc disease .

B.1.2 *Primary objective and endpoint*

Primary objective: To demonstrate that DDD patients operated for spondylolisthesis fare equally well regardless of the surgical procedure (anterolateral or posterior) performed as measured by the improvement of Oswestry Disability Index (ODI) at 3 months as compared to baseline.

Primary endpoint: Improvement of disability at 3 months post-operatively as compared to baseline.

In this prospective study design, patients will be enrolled in one of the 6 procedure groups: ALIF, OLIF, DLIF, PLIF, TLIF or MIDLF. Patients treated with an ALIF, OLIF or DLIF procedure will be assigned to the anterolateral procedure group and patients treated with a PLIF, TLIF or MIDLF procedure will be assigned to the posterior procedure group.

- **Rationale for primary endpoint selection**

The accuracy of an outcome instrument is dependent on its reliability, validity and responsiveness (5). The rationale for selecting the Oswestry Disability Index (ODI) is that it is reliable, accurate and has a good responsiveness, in addition it is translated to several languages and validated.

The Oswestry Disability Index (ODI) was used to assess pain and disability in the original MASTERS-D trial (NCT01143324), and is one of the principal instruments for managing outcomes in spine disorders, including lumbar fusion techniques in patients with chronic low-back pain disorders. The ODI is registered with the International Consortium for Health Outcome Measures as a standard outcome measure (55, 56). It is spine-specific, considered as the “gold standard” by several systematic reviews (4, 56, 57) and recent surgery guidelines(5), validated for different languages, used in numerous randomized controlled trials and long-term follow up studies(3, 58), for different follow-up periods (57, 59, 60). It has been shown that the smallest change score to represent a real change beyond measurement error with 95% probability in one individual (MDC_{95}) is 11.75, with SEM (standard error of mean) of 4.24(4). The ODI score was able to detect clinically relevant changes (61) after surgical treatment for low-back pain. Clinical relevant changes were evident also when the ODI was used to compare MIS techniques with each other or with open surgery techniques (3, 62). The highly cited SPORT-study used the ODI for its consistency with interpretation of the SF-6D (63-65) in comparing surgical with non-operative treatment in patients with intervertebral disc herniation, spinal stenosis, and degenerative spondylolisthesis. Furthermore, ODI was also used to generate utility values(6) in lumbar fusion patients.

SWESPINE, the Swedish national Spine register, is reporting outcomes related to lumbar spine disorders treated in patients diagnosed with disc herniation, spinal stenosis, spondylolisthesis and degenerative disc disease and

treated with lumbar surgery over the last 20 years. Significant functional disability improvements from baseline measured by the ODI score were reported at 1-, 2-, and 5-year follow-up data. The results seemed to be stable over time(66). Results from the MASTERS-D study showed that significant improved outcomes could occur much earlier (9), in patients with degenerative lumbar disorders treated with minimally invasive lumbar interbody fusion (MILIF). The present study aims to further investigate the effects of MILIF surgical techniques, while also having a pathology based approach.

This study intends to investigate functional improvements that occur at 3 months post-surgery, in patients with spondylolisthesis, treated by a minimally invasive surgery technique, thus adding to the existent body of evidence. Secondary outcomes, for patients diagnosed spondylolisthesis at longer follow up, and for patients diagnosed with stenosis, with/without spondylolisthesis, are also aimed to be reported at different follow up intervals(16).

B.1.3 *Secondary objectives and endpoints*

1. To evaluate whether DDD patients without spondylolisthesis fare equally well regardless of the surgical procedure (anterolateral or posterior) performed, as measured by Oswestry Disability Index (ODI) at 3 months

2. To observe and document clinical and radiological outcomes through 5 year follow-up (except for ODI at 3 months)
   - Endpoints:
     a) Improvement of ODI as compared to baseline
     b) Improvement of VAS back- and leg pain intensity as compared to baseline
     c) Improvement of EQ-5D as compared to baseline
     d) Neurological success
     e) Fusion success
     f) Secondary Surgeries at index and/or adjacent level(s)
     g) Adverse Events

3. To observe and document the patients' short term recovery after surgery
   - Endpoints:
     a) Time needed for first ambulation: Days needed for patient to get out of bed and ambulate with or without assistance
     b) Surgery Recovery Day: Days after the surgery, fulfilling following criteria:
        i. No need for intravenous infusion of analgesic drugs
        ii. No ongoing surgery related adverse events impeding discharge
        iii. No need for nursing care

4. To document health resources consumption and perform economic analyses.

5. To observe and document the patient profile when choosing a particular minimally invasive fusion procedure.

The primary endpoint and the secondary endpoints outlined in secondary objectives 2 and 3 of will be analyzed for all DDD patients and the following subgroups:

1) In DDD patients with spondylolisthesis and stenosis
2) In DDD patients with spondylolisthesis but without stenosis
3) In DDD patients with stenosis but without spondylolisthesis
4) All patients not included in subgroup 1), 2), 3).

The grade of spondylolisthesis will be evaluated according to the Meyerding grading system (Grade I < 25%, Grade II is 25-49%, Grade III is 50-74% and Grade IV is 75-99% sagittal slip, Grade V if the vertebral body completed slips from the body below (spondyloptosis)).

- **Rationale for selection of the secondary endpoints**

VAS back / leg pain

The study requires an assessment of the level of pain and pain like symptoms in the back and the legs. Although quantification of pain remains a great challenge, patient completed visual analogue scales (VAS) are the preferred method to quantify pain or the changes thereof. Thus VAS is used in our study as well to quantify pain and pain like symptoms in the back and legs.
The study utilizes VAS in order to assess the magnitude and the eventual changes in these two pain types.
A standardized visual analogue scale (VAS, 0-10) will be used to evaluate the level of intensity of leg and back pain as perceived by the patient, where 0 is no pain and 10 is the worst pain possible.

EQ-5D questionnaire

Health-related quality of life will be assessed by using the five-item EQ-5D questionnaire at the study center, with three levels for each dimension: no problems, some problems, or extreme problems. EQ-5D index scores will be obtained using the UK population value set (http://www.euroqol.org). The EQ VAS will also be utilized to document the patient's self-rated overall health state on a 0 to 100 scale (0 = maximal health-related problems, 100 = minimal health-related problems).

Generic tools such as Euroqol (EQ-5D) are currently used in spine surgery practice due to several advantages(67). The score has been validated in different populations, diseases, setting and for different languages, allowing comparisons(68). Moreover, it allows the evaluation of cost-effectiveness(68). EQ-5D is increasingly used in spinal research(69-71), and it has outcomes in spinal surgery(4, 69, 70).

Neurological status

Neurological status will be evaluated both prior to the surgery and throughout the study.
Neurological status is based on four types of measurements (sections): motor, sensory, reflexes, and straight leg raising. Each of the sections is comprised of a number of elements. Following scales will be used to evaluate neurological status: reflexes (0 = Absent or Trace, 1 = Hyper-reflexic, 2 = Normal), sensory function (Light Touch or Pin Prick L1 to S1), motor function (using 0-5 scores 0-5 whereas 0= Total Paralysis, 1 = Palpable or Visible Contraction, 2 = Active Movement, Gravity Eliminated, 3 = Active Movement, Against Gravity, 4 = Active Movement, Against Some Resistance and 5 = Active Movement, Against Full Resistance (full strength) and straight leg raise (positive = patient experiences radiating leg pain below the knee on elevating the leg between 15 and 70 with the knee extended, normal = no pain is experienced on elevating the leg between 15 and 70 with the knee extended).
Overall neurological success will be defined as maintenance or improvement in all sections (motor, sensory, reflex, and straight leg raising) for the time period evaluated. In order for a section to be considered a success, each element in the section must remain the same or improve from the time of the baseline evaluation to the time period evaluated. Therefore, if any one element in any section does not stay the same or improve, then a patient will not be considered a success for neurological status.

Fusion

From the surgical point of view, fusion is the main target of performing the procedure.

Fusion will be assessed at 1 year, preferably by collecting a CT-scan, alternatively fusion may also be collected thru X-Rays. If no fusion is observed during the first fusion assessment further fusion assessment(s) will be at the discretion of the investigator. The criterion for fusion when assessed thru a CT-scan is bony bridging and when assessed thru X-Rays the criteria are bony bridging, no motion (<4˚) in Flexion/Extension views and integrity of

instrumentation (implanted devices). The surgeon or hospital radiologist will determine fusion. Fusion success rate will be summarized at 1, 2, 3, 4, 5 -year follow-up. If a subject shows fusion success at early timepoints and non-fusion at a later timepoint, the fusion status at all earlier points should be considered as non-fusion. For 2-level subjects, fusion success will be defined as achieving fusion at both treated levels.

Proportion of patients needing a second surgery at the index and/or adjacent level(s) (reoperation rates) throughout the study

When a patient requires additional surgery at the index and/or adjacent level(s), it can be an indicator of insufficient outcomes of the initial surgery. As such, this is a reflection of the efficiency of the initial surgery and therefore is of great clinical value to the surgical community and through that to the patients. Due to the progressive nature of the degenerative lumbar spine, additional surgeries at the index and/or adjacent level might be required after the initial surgery. To ensure all safety and economic values are collected, the revision surgeries and their complication types and rates will be assessed during the study as assessed by the surgeons.
In case the investigator or hospital becomes aware of a second surgery at the index and/or adjacent level in another hospital, this should also be documented in the AE eCRF.

Document Adverse Events occurrence throughout the study

The study is designed to observe and document events related to clinical safety and performance of the devices according to approved instructions for use. During the follow up period (up to 5 years), the occurrence of all AEs will be monitored, registered and analyzed. To safeguard the safety of the clinical study subjects, all AEs will be collected even those that may not be directly related to the surgery.

Time in days needed for first ambulation

The time in days needed for first ambulation with or without assistance will be part of clinical outcome measures to document the patient's short term recovery of the surgery. Ambulation will be defined in this study as ability to walk with or without assistance.

Surgery Recovery Day

The objective of the Surgery Recovery Day assessment is to collect the day when the patient could be discharged based on his actual clinical condition because the effective day of discharge may be prolonged by factors other than the patient's clinical recovery such as social factors or co-morbidity.

For the purpose of reporting these parameters the day of the surgery will be considered 'D0', the first day after surgery as 'D1', the second day as 'D2' and so on.

B.1.4 *Additional Measurements*

Other measurements in the study will be co-morbidities, hospital discharge day, rehabilitation program, pain medication consumption throughout the study, days to first return to work, additional medical visits related to back pain, sagittal balance.

Co-morbidities

Comorbidities can be either medical condition(s) existing simultaneously but independently with another condition; or it can indicate a related medical condition or conditions. Comorbidities may affect the outcomes of the surgery.

Hospital Discharge Day

Days after the surgery when patient has been discharged from hospital.

Rehabilitation program

Information on the rehabilitation venue and program will also be collected in order to assess how many patients will have rehabilitation in an in-patient setting, at home or in an outpatient rehabilitation unit. Corresponding costs will be evaluated and included in the economic analyses.

Pain Medication consumption throughout the study

When assessing the economical outcomes after surgical treatments in chronic diseases such as Degenerative lumbar spine, it is essential that pain medication consumption of the patients is also collected.

Days to first return to work

Information on the days needed to first return to work will also be collected by the patient for the investigator in order to assess how long it takes for patients to return to work. Corresponding costs will be evaluated and included in the economic analyses.

Additional Medical visits

Information on additional medical visits related to the spine that are not related to the study protocol will be collected throughout the study (e.g. outpatient consultations, visits to primary care services, visits to general practitioner).

Sagittal Balance

Collection of Sagittal Balance parameters can show us if the patient's spine is balanced or not prior to or after the surgery. Any evolution of parameters after the surgery can indicate a change in Sagittal Balance or a mechanism of regulation / compensation due to an evolution of the spinal alignment. Sagittal balance parameters may include Pelvic Incidence, Sacral Slope, Pelvic Tilt, Global Lordosis Angle, Lordosis Apex Location and Inflection Point Limit.

Sagittal balance data will be assessed by the investigator and only be collected by the sites if it is part of standard of care at the hospital.

DN4 questionnaire, (Douleur Neuropathique 4 (neuropathic pain))

The French Neuropathic Pain Group developed a validated clinician-administered questionnaire named DN4 consisting of both sensory descriptors and signs related to bedside sensory examination(72). Identification of neuropathic components is important for characterization of chronic pain patients. The 10 questions are answered by subject interview and clinical examination. The first seven items are related to the quality of pain (burning, painful cold, electric shocks) and its association to abnormal sensations (tingling, pins and needles, numbness, itching). The other 3 items are related to neurological examination in the painful area (touch hypoesthesia, pinprick hypoesthesia, tactile allodynia). A score of 1 is given to each positive item and a score of 0 to each negative item. The total score is calculated as the sum of all 10 items. A score of at least 4/10 in this questionnaire is indicative of neuropathic pain, with excellent sensitivity and specificity (73). Two questionnaires will have to be completed, one will be completed to address the neuropathic pain specifically in the leg and one specifically in the back.

Additional spinal cord stimulation or pain pump

When a patient requires spinal cord stimulation or pain pump, this should also be documented in the AE CRF.

B.2 Study Population

Patients enrolled in this study will receive a single or double level instrumented fusion using minimally invasive PLIF, TLIF, MIDLF, DLIF, OLIF or ALIF procedures. Please see a list of abbreviations at section K.4 of this protocol.

B.3 Definitions Study Procedures

In order to make a clear distinction between the different techniques the following definitions will apply:

For the posterior procedures:

- TLIF: Fusion Procedures targeting the disc space with a trajectory lateral to the medial pedicle wall.
- PLIF: Fusion procedures targeting the disc space with a trajectory medial to the medial pedicle wall (in the coronal plane).
- MIDLF: Fusion procedures with a medial to lateral pedicle screw trajectory deep to the segmental back muscles and with the screw construct placed into the pedicle through cortical bone. Fixation, decompression, and interbody fusion through a laminectomy approach.

For the anterolateral procedures:

- DLIF: Fusion Procedures with a Lateral Transpsoas approach via a smaller incision and dilatation. This technique would also be named Lateral Lumbar Interbody Fusion in literature.
- OLIF:
  - OLIF25: Access to L2-L5, approach via oblique corridor between the aorta and the psoas avoiding the lumbar plexus and iliac crest.
  - OLIF51: Access to L5-S1, approach via oblique corridor between the iliac vessels
- ALIF: Anterior incision, transperitoneal or retroperitoneal approach. Disc access L4-L5 or L5-S1.

B.4 Study hypothesis

The study hypothesis for the primary objective is to verify whether DDD patients operated for spondylolisthesis (≥ grade I) have equivalent mean improvement of ODI at 3 months regardless of the minimally invasive surgical procedure (anterolateral or posterior) used.

More specifically:

The null-hypothesis;

H_o: $\Delta_{ODI\_Anterolateral} \neq \Delta_{ODI\_posterior}$

will be tested against the alternative hypothesis

H_A: $\Delta_{ODI\_Anterolateral} = \Delta_{ODI\_posterior}$

Where $\Delta_{ODI\_Anterolateral}$ is the average improvement in ODI score (baseline - 3 months) in spondylolisthesis DDD subjects treated with the anterolateral approach and $\Delta_{ODI\_posterior}$ is the average improvement in ODI score (baseline - 3 months) in spondylolisthesis subjects treated with the posterior approach.

The study hypothesis for the first secondary objective is to verify whether DDD patients operated for non-spondylolisthesis have equivalent mean improvement in ODI at 3 months regardless of the minimally invasive surgical procedure (anterolateral or posterior) used. More specifically:

The null-hypothesis;

H_o: $\Delta_{ODI\_Anterolateral} \neq \Delta_{ODI\_posterior}$

will be tested against the alternative hypothesis

H_A: $\Delta_{ODI\_Anterolateral} = \Delta_{ODI\_posterior}$

Where $\Delta_{ODI\_Anterolateral}$ is the average improvement in ODI score (baseline - 3 months) in non-spondylolisthesis subjects treated with the anterolateral approach and $\Delta_{ODI\_posterior}$ is the average improvement in ODI score (baseline - 3 months) in non-spondylolisthesis subjects treated with the posterior approach.

There is no hypothesis testing for other secondary objectives with descriptive nature for the analyses.

B.5 Study design

The MASTERS-D 2 study is a Prospective, Global clinical trial. Commercially available study devices will be used within their intended use.

The indication for the treatment of a patient will be at the discretion of the surgeon.
As such the assignment of a patient to a particular surgical intervention is not required within this clinical study protocol but falls within standard of care practice.

All fusion procedure patients will be screened consecutively against the eligibility criteria. Every effort will be made to enroll subjects in a consecutive manner.
Study enrollment is open to eligible subjects who in the opinion of the investigator are candidates for a minimally invasive lumbar fusion surgery.

The investigator or authorized designee must obtain written informed consent/ data release consent from the patient before any clinical study related activity takes place. The patient has the right to refuse and refusal will not affect the care of the patient. The patient can opt out at any time from the study. Refusal of study participation as well as enrollment into the study will be recorded on the screening log.

The following measures have been taken to avoid bias:

- Consecutive screening and enrollment is encouraged and enforced as much as possible.
  - When all inclusion/exclusion criteria are fulfilled for a patient, then the patient should be enrolled in this study. A screening log will be maintained at each site documenting the patients that have been screened and identified to be eligible or ineligible for the study, declined patients and enrolled patients.
  - In case the group with one of the approach procedures has reached the maximum amount of patients per procedure in a specific region, further enrollment of subjects into the procedure will be terminated. An email will be sent to the participating sites to inform the investigators when the enrollment for a specific procedure is complete.
- A multi-center design is used to help ensure a representative sample of surgeons performing the procedure and to ensure a reasonable enrollment period
- Only surgeons that have adequate experience (> 30 minimally invasive lumbar fusion procedures) can participate
- Site training will be performed to assure full understanding and engagement to comply with the study design and all protocol requirements
- Preferably, the ODI outcome measurements at 1, 3 months and 1, 2, 3, 4, 5 year follow up will be done by site staff different than the surgeon who operated the patient. The site staff will be trained to collect the ODI outcome measurements in an independent way without influencing the patients.

B.6 Randomization and blinding

Randomization and blinding is not applicable in this study.

B.7 Sample size

The primary objective is to evaluate if DDD patients operated for spondylolisthesis fare equally well regardless of the surgical procedure (anterolateral or posterior) performed, measured by the improvement of Oswestry Disability Index (ODI) 3 months after the surgery.

For the initial sample size calculation "equally well" was defined as a difference in ODI improvement at 3 months between groups within the range of (-7.5, 7.5) points. However, taking into account literature (74, 75) and the opinion of the Study Advisory board the equivalence range was increased to (-10, 10) points. As patient enrollment is slower than initially forecasted, the increase in equivalence range also allows completing enrollment timely

If the difference in ODI improvement at 3 months between the anterolateral procedures group and the posterior procedures group is within the range of (-10, 10) points, the anterolateral and posterior treatment options will be considered equivalent in terms of effectiveness.

Assuming that the standard deviation for ODI improvement at 3 months is 20 for both groups (anterolateral and posterior) and there is no difference in the mean ODI improvement at 3 months, with 80% power and 5% alpha level, the sample size per group is 70 in order to claim equivalence of the primary endpoint between two groups with equivalent margin (-10, 10)

Estimated sample size per group (anterolateral procedures versus posterior procedures):	70
Estimated total sample size for spondylolisthesis patients with DDD:	140

From the MASTERS-D study it is known that approximately 50% of the patients with degenerative disc disease have spondylolisthesis ≥ grade I. Hence the required total sample size is 140/0.5 = 280.

The study is anticipated to enroll 350 patients. The amount of patients with spondylolisthesis versus non-spondylolisthesis will be monitored during the study. In case the study team identifies that the target amount of spondylolisthesis patients for the anterolateral procedures and posterior procedures might not be reached, the sites might receive instruction to limit the enrollment of non-spondylolisthesis patients. This action will secure the enrollment of target sample size as calculated for the primary endpoint. Additionally, it might be decided to stop patient enrollment completely when the required sample size for the primary endpoint has been reached.

It is expected that approximately 350patients will be enrolled in this study from approximately 30 sites in Europe, Middle East, Latin America and Asia Pacific. This study will be open for enrollment to other countries in order to meet the required patient numbers. Sites have been selected based upon an anticipated enrollment for each minimally invasive fusion procedure. Consecutive enrollment will apply per minimally invasive procedure (i.e. ALIF, OLIF, DLIF, PLIF, TLIF and or MIDLF).

To allow the different regions to contribute patients to this study, a maximum enrollment per country/region might be defined during the course of the study This will be timely communicated to the investigators and they will be requested to stop enrollment when the country/regional anticipated maximum number of patients has been reached. Patient enrollment limits per site for each country/region are indicated in Table 1. These limits may be subject to change during the course of the study and will be communicated as appropriate to the investigators and EC/IRB, if required.

The distribution of the procedures differs among the regions. Patient distribution accross different surgical procedures will be in accordance with natural distribution in the country, but the study will aim to balance the

subjects between the procedures. Nevertheless, a minimum enrollment of 20 patients in each procedure (ALIF, OLIF, DLIF, PLIF, TLIF or MIDLF) is required for the study. A broad usage of both anterolateral and posterior lumbar fusion procedures is encouraged at all sites even though it is acknowledged that a user preference will apply. Enrollment limits per procedure have been defined for sites in China as these sites are allowed to enroll more patients than sites in other regions (Table 1). Investigators will be requested to stop enrollment when the maximum enrollment for that procedure at their site has been reached.

Table 2: Overview of patient enrollment limits in Europe, Latin America, Middle East and Asia Pacific per site and per procedure.

REGION	EUROPE	LATIN AMERICA	CHINA	KOREA
Enrollment max per site	40	20	120	20
Enrollment maximum per procedure for each site*	40	20	75	20
Estimated Number of sites	21	3	3	3

* Enrollment limits per procedure might change to obtain a better distribution of procedures amongst the sites and regions and reach the minimum enrollment of 40 patients in each procedure. Any change in enrolment limitations will be communicated to the sites.

B.8 Number of investigation sites and study duration

Approximately 350patients will be enrolled over a period of around 4 years in approximately 30 sites located in Europe, Latin America and Asia Pacific. This study is open to other countries/regions as long as the Devices are approved for market release in those countries with the same indications as in the European Community. As the patients will be followed during a period of 5 years after the surgical procedure, the total duration of the study will be of approximately 9 years. Depending on enrolment progress, study timelines are subject to change.

A list of participating investigation sites and investigators will be kept separate from this CIP at the sponsor's Project Files and the Investigator Site Files. The sponsor will keep this list up to date.

C SUBJECT SELECTION

C.1 Inclusion and exclusion criteria

The **Inclusion Criteria** for this study are:

- Patient is ≥ 18 years of age (or minimum age as required by local regulations)
- Patient has degenerative disc disease and an indication for a single or double level instrumented lumbar fusion for the treatment
- Patient agrees to participate in the study and is able to sign the Data Release Form/Informed Consent
- The procedure planned for the patient complies with the labeling of the Devices that may be used in the surgical procedure as described in the section **Device information** above
- Patient is planned to be submitted to a minimally invasive fusion procedure using a **posterior** (**PLIF, TLIF, MIDLF)** or **anterolateral (OLIF, ALIF, DLIF**) technique*.
- The patient is willing and is able to perform study procedures and required follow-up visits.

* For a double level instrumented fusion, the same procedure must be used for both levels.

The **Exclusion Criteria** for this study are:

- Patient that has already undergone a lumbar fusion surgery
- Patient that has already undergone open lumbar surgery other than standard decompression surgery
- Indications for the procedure other than degenerative spine disease like: Osteoporotic vertebral fractures, Spine trauma fractures or Spine tumor
- Illiterate or vulnerable patients (e.g. minors, participants incapable of judgment or participants under tutelage)
- Concurrent participation in another clinical study that may confound study results.

D STUDY PREPARATION PROCEDURES

D.1 Investigator/Investigation site selection

The role of the principal investigator is to implement and manage the day-to-day conduct of the clinical study as well as ensure data integrity and the rights, safety and well-being of the subjects involved in the clinical study. Sites will be nominated and selected for this study based upon screening against a list of selection criteria. Compliance with the components of the list is intended to ensure high quantity and quality data. An investigation site may be included in this study if the investigation site complies with the following requirements:

- The operating study surgeons must have a minimum previous experience of at least 30 instrumented minimally invasive lumbar interbody fusion procedures for degenerative lumbar spine indications.
- The operating study surgeons must have recognized expertise in at least one of the surgical techniques which are the objective of this study PLIF, TLIF, ALIF, OLIF, DLIF and/or MIDLF
- Site must have sufficient patient population
    - Annual Case volume of > 30 minimally invasive lumbar fusion procedures
    - Ability to enroll at least 10 patients over a period of 12 to 18 months.
- Investigator must have interest in clinical research and motivation to participate in the study.
- Site will assess fusion at 1 year FU by CT scan or X-Rays as standard of care.
- Investigator should have adequate staff that has time to perform data collection and electronic data capture.
- Investigator and his study staff must be willing to comply with applicable regulations and this Clinical Investigation Plan (Protocol).
- Have internet connection at the site with sufficient data transfer speed to facilitate data entry in the web based eCRFs.
- Willing to undergo monitoring and auditing by sponsor or relevant regulatory authorities
- Willing to undergo required study training
- Willing to enroll subjects in a consecutive manner

In addition, the site and Investigators will also be selected based on geographic location and/or previous participation in the MASTERS-D study.

D.1.1 *Clinical Investigation Agreement*

A Clinical Investigation Agreement shall be in place, signed by the participating investigation site and/or principal investigator of each investigation site, as per the local legal requirements, and returned to Medtronic prior to the commencement of any clinical study activities. The investigator is indicating approval of the Clinical Investigation Plan and subsequent amendments, by a fully executed agreement. Amendments to this Clinical Investigation Plan

shall be agreed upon between Medtronic and investigator(s) and be recorded with a justification for the amendments.

D.1.2 *Curriculum Vitae*

Prior to study start, an up to date signed and dated curriculum vitae shall be collected from each investigator participating in this clinical study, evidencing the required qualifications, including the year and where obtained, and shall include their current position at the investigation site. The signature on the CV must be dated within 3 years prior to the date of activation of the site.

D.2 Ethics

All patients enrolled in this study must be able to give the Data Release or Patient Informed Consent whichever is applied.

D.2.1 *EC/IRB approval*

EC/IRB approval depends on local law/hospital requirements. If not required by the hospital, written documentation from the investigator is required. However, when the sponsor is responsible for EC submission, a written documentation from the sponsor is required.

EC/IRB requirements may vary from site to site and from country to country. This is especially applicable for studies under the scope of a post market release design.

Some EC/IRB will require a full submission of the study documentation including a Patient Informed Consent Form or Data Release Form and will inform the investigator in writing that there are no objections to start the study after a review according to their procedures. Other EC/IRB might only require to be notified about the planned conduct of this study, while some sites do not require EC/IRB involvement to start the study.

It is the responsibility of the investigator to confirm the approval requirements of the hospital and local regulations for this study with his/her EC/IRB prior to start this study.

In case EC/IRB approval is required per local law/ hospital regulations:

Prior to enrolling subjects in this clinical study, the investigation site's EC/IRB will be required to approve the current Clinical Investigation Plan, the Patient Information and Informed Consent form. EC/IRB approval of the clinical study must be received in the form of a letter and provided to Medtronic before commencement of the clinical study at an investigation site. The approval letter must contain enough information to identify the version or date of the documents approved. If this information is not contained in the approval letter, it must be retrievable from the corresponding submission letter. In addition, the approval letter needs to be accompanied by an EC/IRB roster or letter of compliance, to allow verification that the investigator, other investigation site personnel, and/or Medtronic personnel are not members of the EC/IRB. If they are members of the EC/IRB, written documentation is required stating that he/she did not participate in the approval process. If the EC/IRB imposes any additional requirements (e.g. safety reports, progress reports etc.), Medtronic will prepare the required documents and send them to the investigator for reporting to the EC/IRB. Investigators must inform Medtronic of any change in status of EC/IRB approval once the investigation site has started enrollment. If any action is taken by an EC/IRB with respect to the investigation, that information will be forwarded to Medtronic by the respective investigator.

In case EC/IRB notification is required per local law/ hospital regulations:

For investigation sites in which the local EC/IRB only needs to be notified about this study, the investigator needs to provide a copy of the EC/IRB notification letter to Medtronic prior to enrolling subjects in the clinical study. For the initial submission and any subsequent CIP amendment, the investigator needs to sign a statement (available

at **Appendix K.6**) confirming that this approach is in accordance with local regulations. However, when the sponsor is responsible for EC submission/notification, written documentation from the sponsor is required.

In case neither EC/IRB notification nor approval is required per local law/ hospital regulations

If neither approval nor notification from the EC/IRB is necessary to conduct the study at the investigator's hospital, written documentation from the investigator is required. However, when the sponsor is responsible for EC submission/notification, a written documentation from the sponsor is required.

For the initial submission and any subsequent CIP amendment, the investigator needs to sign a statement (available at **Appendix K.6**) confirming that this approach is in accordance with local regulations prior to start patient enrollment. A copy of this statement needs to be forwarded to Medtronic prior to the start of patient enrollment.

D.2.2 *Informed consent process*

If full Informed Consent (other than the Data Release Consent) is requested by local laws or by the EC/IRB, the investigator or authorized designee must obtain written informed consent from the subject and the process must be documented before any clinical study related activity takes place.

A "Patient Informed Consent" document will be developed specifically for each country, approved by the EC/IRB in the local language.

Well in advance of the consent discussion, the subject should receive the EC/IRB approved Patient Information and Informed Consent Form. During the consent discussion, the investigator or his/her authorized designee must fully inform the patient of all aspects of the clinical study that are relevant to the patient's decision to participate in the clinical study. All items addressed in the Patient Information and the Informed Consent Form must be explained. The language used shall be as non-technical as possible and must be understandable to the patient.

The patient must have ample time and opportunity to read and understand the Patient Information and the Informed Consent Form, to inquire about details of the clinical study, and to decide whether or not to participate in the clinical study. All questions about the clinical study should be answered to the satisfaction of the patient.

Neither the investigator, nor the investigation site staff shall coerce or unduly influence a patient to participate or to continue to participate in the clinical study. The informed consent process shall not waive or appear to waive the patient's rights.

When the patient decides to participate in the clinical study, the Informed Consent Form must be signed and personally dated by the patient and investigator or authorized designee.

After all persons have signed and dated the Informed Consent Form, the investigator must provide the subject with a copy of the Patient Information and the signed and dated Informed Consent Form.

The clinical study data can only be submitted to Medtronic upon fully execution of the Patient Informed Consent Form.

The signed consent forms will be retained by the investigator and made available (for review only) to the study monitor and inspector or auditor on request.

D.2.3 *Revisions in Patient Information and Informed Consent Form*

Medtronic will inform the investigators whenever new information becomes available that may be relevant to the subject's confirmed participation in the clinical study. The investigator or his/her authorized designee should inform the subject in a timely manner.

Medtronic will revise the written Patient Information and Informed Consent Form whenever new information becomes available that may be relevant to the subject's confirmed participation in the clinical study. The revised information will be sent to the investigator for approval by the EC/IRB if applicable. After approval by the EC/IRB,

a copy of this information must be provided to the participating subjects, and the informed consent process as described above needs to be repeated. However, in case the revised Informed Consent has no impact on previously enrolled patients, the Informed Consent won't need to be re-signed by already enrolled patients.

D.2.4 *Data Release Consent process*

If Data Release Consent is requested by local laws or by the EC/IRB, the investigator or authorized designee must obtain written Data Release Consent from the patient and the process must be documented prior to releasing any personal information of the patient.

During the consent discussion, the investigator or his/her designee must fully inform the patient of the clinical study in a non-technical wording understandable for the patient.

The patient must have ample time and opportunity to inquire about details of the clinical study, and to decide whether or not to participate in the clinical study. All questions about the clinical study should be answered to the satisfaction of the patient.

When the patient decides to participate in the clinical study, the written Data Release Consent form must be signed and personally dated by the patient and the investigator.

After all persons have signed and dated the Data Release Consent Form, the investigator must provide the patient with a copy of the signed and dated Data Release Consent form.

The clinical study data can only be submitted to Medtronic upon fully execution of the Data Release Consent Form.

D.2.5 *Regulatory notification / approval*

The need for regulatory notification or submission is country-specific. The Medtronic study team will work together with the Medtronic regulatory department to identify the requirements per country.

In countries where submission to the regulatory authority is required per local law, no patients will be enrolled in the clinical study until the particular regulatory authority has approved the current Clinical Investigation Plan of the clinical study and other documents as required according to the local requirements.

D.3 Regulatory compliance

This clinical study will be conducted in compliance with the Declaration of Helsinki 2013, laws and regulations of the country/ies in which the clinical study is conducted, including data protection laws, the Clinical Investigation Agreement and the Clinical Investigation Plan.

All principles of the Declaration of Helsinki have been implemented in this clinical study by means of the patient informed consent process, EC/IRB approval (if applicable), clinical study training, clinical trial registration, preclinical testing, risk benefit assessment, publication policy, etc.

All Medtronic Devices to be used in this study will be used within their intended use as described in the manual and Instructions for Use for which Medtronic obtained regulatory market release e.g. CE Marking in Europe. All Devices that can be used in this study are listed in section A.2.

Only legally competent patients will be included in this post market release study.

If the regulatory authority and/or EC/IRB imposes any additional requirements (e.g. safety reports, progress reports etc.), Medtronic will prepare the required documents and send them to the respective authority and/or EC/IRB. If any action is taken by a EC/IRB with respect to the investigation, the information will be forwarded to the sponsor.

D.4 Training requirements

Prior to investigation site activation or subsequent involvement in clinical study activities, Medtronic will provide clinical study training relevant and pertinent to the involvement of personnel conducting clinical study activities and investigator responsibilities.

At a minimum, training will consist of the following items:

- CIP overview and timeframes
- Patient eligibility criteria
- PIC/DRF procedure and documentation in the patient's medical record,
- Consecutive enrollment-screening log
- AE reporting
- Source document requirements
- Use of data collection tools (EDC training)
- Applicable local regulations
- Collect ODI questionnaire in an independent way without influencing the patients.

Performed training will be documented prior to investigation site activation.

After initial training, trained clinical site personnel can provide training to other clinical site study team members on study documents and processes on which they have already been trained on. All training must be documented. The name of each member of the investigational site team that attended the training session must be recorded as well.

An investigator in this protocol is defined as a surgeon who is trained on the protocol training requirements and listed on the site delegation list.

D.5 Site readiness

Before a study site can enroll a subject or have access to the electronic data capturing (EDC) system, the investigator must be in receipt of an 'activation letter' (this may also be an email) from Medtronic. In addition, proper documentation must be in place before site activation, both at the participating site and at Medtronic, before subject enrollment begins.

D.6 Study materials and study-specific equipment

Medtronic will provide study materials such as the Investigator site file required to conduct the clinical study.

Device accountability and traceability is not required for Post Market Release (PMR) studies. The Devices used in this study are commercially available. All Devices need to be purchased by the sites as routinely done. The Devices will be used within the intended approved indication (IFU). Existing approved procedures for commercial product regarding distribution, shipment, storage, handling, and return of these Devices will be followed.

E STUDY METHODS

All assessments to be done at the different time intervals are described in Table 2

Table 3: Description of Procedures and Assessments at different time intervals

Pre-operative visit (Baseline):	• Written Patient Informed Consent /Data Release Form • Demographic data • Medical history • Work status • Pain medication

	• VAS Back and leg pain • ODI • EQ-5D • Neurological status • AP & Lateral Radiographic Evaluation • Imaging (MRI and/or CT Scan) • Sagittal balance (in those sites where this assessment is Standard of care) • DN4 for back and DN4 for leg**
Surgical procedure:	• Surgery procedure data • Surgery time • Blood loss and Transfusion • Device Models • Adverse Events
Hospital stay and discharge: **(Surgery = Day 0)**	• Length of hospital stay (in days) • VAS Back and leg pain (at Day 2, the day the patient is considered recovered from the surgery(=SRD) and/or Day of discharge) • Time in days to first ambulation • Surgery Recovery Day • Record pain medication • Adverse Events
Postoperative assessment at **4w (±2w):** **3m (-1.5/+3m)**	• VAS Back and leg pain • ODI • EQ-5D • Neurological Status • Work Status and rehabilitation program • Pain medication • Adverse Events • Sagittal balance (in those sites where this assessment is standard of care) • DN4 for back and DN4 for leg (at 3m only)**
Postoperative assessment at **1, 2,3, 4 and 5y (±6m)**	• VAS Back and leg pain • ODI • EQ-5D • Neurological Status • Work Status and rehabilitation program • Pain medication • Adverse Events • Fusion Status * • Sagittal balance (in those sites where this assessment is standard of care) • DN4 for back and DN4 for leg (at 1 year only)** • CT-scan or alternatively an X-Ray will be taken to observe fusion 1 year after the surgery. If no fusion is observed during the first fusion assessment further fusion assessment will be at the discretion of the investigator. • ** As DN4 questionnaire has been added in the CIP amendment 2.0, the patients who were enrolled under CIP version 1.0 will NOT complete the DN4 retrospectively but will complete the DN4 questionnaires for any upcoming follow up visits.

E.1 Screening

Every effort will be made to screen subjects consecutively for treatment and enrollment into the MASTERS-D 2 global clinical study. Consecutive enrollment per procedure is essential in order to minimize selection bias.

When all inclusion/exclusion criteria are fulfilled for a patient, then the patient should be enrolled in this study. Failure to meet all inclusion and exclusion criteria results in a screening failure and such subjects must not be enrolled to the study.

A subject screening log is provided to the site and should be completed by the site's study staff to maintain a cumulative log of all screened subjects per procedure. Patients not suitable for the study or refusal to participate should also be collected and reported in the subject screening log kept at each sites and reported at end of study recruitment. The Investigator will maintain a Subject Identification & Enrollment Log of all subjects enrolled in the clinical investigation, assigning a subject study ID linked to their names. Patient identifier will not leave the hospital. In case the group with one of the procedures is completed in a specific region, further enrollment of subjects into the procedure will be terminated, an email will be send to the participating sites when the enrollment for a specific procedure is complete. Once a procedure group is complete or the site maximum capacity of enrollment has been reached, no further screening will occur at the site for the applicable procedure.

E.2 Point of enrollment

A subject is considered enrolled in this clinical study at the time at which he/she signed the Informed Consent Form or Data Release Consent form (whichever is applicable, see section D.2 Ethics).

The investigator will maintain a log of all subjects enrolled in the clinical investigation, assigning an identification code linked to their names, alternative subject identification or contact information.

All subjects must sign the Informed Consent Form or Data Release Consent form (whichever is applicable, see section D.2 Ethics) prior to undergoing any evaluations or procedures that are purely research-related (defined as those that would not be done if the subject was not participating in this study) or collection of study data.

E.3 Baseline procedures

During the baseline visit the following data will be collected, patient demographics, medical history, comorbidities, surgery indication, pain medication, work status, imaging data. A standardized visual analogue scale (VAS, 0-10) will be used to evaluate the level of leg and back pain as perceived by the patient prior to surgery. Quality of life will be assessed having the patient completing the EQ-5D. Evaluation of how back or leg pain is affecting the patient's ability to manage in everyday life will be assessed using the Oswestry Disability Questionnaire (ODI). Neurological status; in case of a neurological abnormality, the neurological status will be assessed and documented. The measurement of Slip and Disk Height of the levels adjacent to the index level(s) will be collected by X-Ray, CT scan and/or MRI whichever is applicable at the site. The identification of neuropathic pain will be assessed by the DN4 questionnaire in the back and in the leg.

Sagittal Balance will be collected in those sites where it is standard of care by collecting an X-Ray (preferably this would be a long standing / full spine X-Ray (C7 + Femoral Head visible) or alternatively a short X-Ray with the femoral heads and top of lordotic segment visible).

AEs should be collected after patient signed consent/data release form.

E.4 Implant or procedure aspects

Patients will receive a single or double level instrumented fusion using a minimally invasive/MAST™ **PLIF, TLIF, DLIF, OLIF, ALIF or MIDLF** surgical procedure with a posterior fixation. The use of a posterior fixation system is mandatory in this study and will be either mini-open and/or percutaneous.

Only those investigators with a documented experience of at least 30 minimal invasive procedures are allowed to perform the procedure of the subjects in this study.

It is recognized that the situation of a patient might change after enrollment. Due to investigator's discretion a patient who was scheduled for a minimally invasive lumbar fusion procedure might receive an open procedure, might not be operated to treat the degenerative lumbar spine or might have a different procedure for other reasons.
It is at the investigator discretion to decide before or during the surgery that the patient does no longer meet the eligibility criteria of the study to perform a Minimally Invasive Fusion Surgery. If this situation occurs this shall be documented on a study deviation eCRF (please see section E.11) and appropriate action should be taken (see section E.10) as well as a rationale for either continuing with the minimally invasive procedure, continuing with an open procedure or for discontinuation of the procedure and the study early termination form will be completed in the eCRF.

E.5 Post Procedure to Discharge

All subjects will be assessed until discharge. Assessments are described in Table 2 .

Day 2 after the procedure, at SRD and at discharge following assessments will be collected:

Pain medication, VAS Leg and Back pain intensity scores, hospital data and AEs.

E.6 Follow up requirements.

The schedule for patient assessments and follow-up visits after surgery (with required windows) will be 4 weeks (± 2 weeks), 3 months (-1.5/+3 month), 1 year (± 6 month), 2 years (± 6 month), 3 years (± 6 month), 4 years (± 6 month), 5 years (± 6 month).
After the closure of the 5 year follow-up visit window patients will be automatically considered as terminated from the study.
All data will be collected via a secure web-based data entry system.

Treatment outcomes in terms of how back or leg pain is affecting the patient's ability to manage in everyday life will be assessed using the Oswestry Disability Questionnaire (ODI). Preferably, these ODI outcome measurements at 1, 3 months and 1, 2, 3, 4, 5 year follow up will be done by site staff different than the surgeon who operated the patient.

A standardized visual analogue scale (VAS, 0-10) will be used to evaluate the level of leg and back pain as perceived by the patient.
Quality of life will be assessed having the patient completing the EQ-5D.
The identification of neuropathic pain will be assessed by the DN4 questionnaire in the back and in the leg at 3 and 12 months follow up.

The measurement of Slip and Disk Height of the levels adjacent to the fused level(s) and fusion will be collected at 1 year follow up with either a CT scan or X-Rays. If no fusion is observed, 1 year after the surgery, further fusion follow up assessment will be at the discretion of the investigator.

Neurological status will also be documented. This is an AE if the patient did not have a neurological abnormality before.

Additional medical visits, Pain medication, work status and rehabilitation program will also be collected as part of overall patient follow up.

Sagittal Balance will be collected in those sites where it is standard of care by collecting an X-Ray (preferably this would be a long standing / full spine X-Ray (C7 + Femoral Head visible) or alternatively a short X-Ray with the femoral heads and top of lordotic segment visible).

Table 2 summarizes assessments and data (variables) to be collected in the electronic-CRFs throughout the study.

E.7 Data collection requirements

Table 2 summarizes what data will be collected prospectively within this study.

After the surgery, regular patient follow up visits will be done to complete the Quality of Life questionnaires and to assess work status, and rehabilitation program.

While a hospital visit is required for the 3 months (-1.5/+3 month) and 1 year (± 6 month) follow up; the Postoperative follow-up assessment at 4 weeks (± 2 weeks), 2 years (±6 months), 3 years (±6 months), 4 years, (±6 months), and 5 years (±6 months) can either be done through a patient visit at the hospital or by means of a phone call done by the investigator and/or authorized designee.

The ODI outcome measurements are preferably done by site staff different than the surgeon who operated the patient. Training will be provided to the site to collect the ODI outcome measurements in an independent way without influencing the patients.

Imaging is critical for assessing fusion. At 1 year follow up, each site should at least perform a CT scan or X-Rays per patient to assess fusion. If no fusion is observed, 1 year after the surgery, further fusion follow up assessment will be at the discretion of the investigator and the investigator will have the opportunity to enter this data in the CRF.

Sagittal Balance will only be collected in those sites where it is standard of care to assess the sagittal balance of the patient.

Calibration and maintenance of imaging equipment should be done according to the instructions of the manufacturer of the equipment and according to local protocols per Institution's standards.

Table 4: Summary of scheduled procedures and assessments

			Hospital Stay and Discharge (3)			Follow up assessments						
	Baseline	Day of Surgery (D0) (2)	D2	SRD	DIS	4(±2)week	3(-1.5/+3)month	1 year (±6 months)	2 year (±6 months)	3 year (±6 months)	4 year (±6 months)	5 year (±6 months)
Data Release Form *OR* Informed Consent Form	X (1)											
Demographics	X											
Medical History	X											
Surgery Indication	X											
Pain medication	X		X	X	X	X	X	X	X	X	X	X
Imaging (X-Ray, MRI and/or CT Scan)	X											
VAS (4)	X		X	X	X	X	X	X	X	X	X	X
ODI	X					X	X	X	X	X	X	X
EQ-5D	X					X	X	X	X	X	X	X
DN4 in the back and DN4 in the leg	X						X	X				
Work status	X					X	X	X	X	X	X	X

Rehabilitation Program						X	X	X	X	X	X	X
Neurological status	X					X	X	X	X	X	X	X
X-Ray or CT Scan (5)								X	(X)	(X)	(X)	(X)
Sagittal Balance(6)	(X)					(X)	(X)	(X)	(X)	(X)	(X)	(X)
Surgery and hospital data		X	X	X	X							
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X

(1) Patient Informed Consent must be obtained prior to performing any study specific procedure

(2) Day '0' (D0) is the day of the surgery, D1 is the first day after surgery, D2 the second and so on.

(3) **SRD** = Surgery Recovery Day; **DIS** = Day of Discharge

(4) VAS Intensity scores for Back and Leg pains.

(5) CT scan or X-Rays at 1 year follow up. If no fusion is observed at 1 year follow-up, it will be at the discretion of the investigator to follow up if fusion can be observed (only if standard of care at the site).

(6) Optional only if it is routine practice (standard of care) at the site

E.8 Source documents

All source documents marked in the eCRFs should be located in the patient's medical records (electronic, digital, or paper), i.e. hospital records, surgery reports, x-rays, MRIs, CTs or any other material that contains original information used for data collection including the documentation of the AEs and study worksheets completed by the investigator or site staff. Patient completed questionnaires will be considered as source data (i.e. VAS pain scores, ODI, EQ-5D, DN4 in the back and DN4 in the leg).

The investigator will clearly mark the medical records to indicate that the subject is enrolled in this clinical study.

For studies conducted in Sweden the investigator should also provide a short explanation on the clinical study (i.e. post market release study with MAST and CD horizon spinal system, treatment: minimally invasive lumbar interbody fusion (1 or 2 level) and 5 years follow-up) in the patient medical records.

In case a follow-up has been performed by phone, the site personel needs to record at a minimum the date of contact in the patient's medical records, the occurrence or absence of any AEs, pain medications for the lumbar spine and any other pain medications and indicate on the questionnaires who was the person that completed them.

In section F.1.2 it is described which source data can be recorded directly on the electronic Case report Forms.

Access to all (including electronic) source documents (medical records and other source data) will be provided to the sponsor and its representatives, EC/IRB, regulatory authorities, if required.

E.9 Adverse events

All AEs, regardless of relatedness to surgical procedure or outcome, should be reported throughout the study in the CRF and should be made available to the Medtronic study team. If applicable, these events will be reported to other countries where studies are conducted with the same or a similar product. All AEs will be screened immediately for possible product complaints, to allow compliance with the 48-hours reporting requirement.

In China, the Clinical safety reporting requirements are governed by the following China Food and Drug Administration (CFDA) documents.

- CFDA Notice No. 766: Measure on Medical Device Adverse Events Monitoring and Reevaluation
- CFDA Guidance document No. 425: Device Adverse Event Monitoring (Interim)

CFDA Notice No. 766 and CFDA Guidance document No. 425 are vigilance reporting requirements in China.

Since there is no country specific clinical safety reporting requirement for this study in China, the common safety reporting process for all participating regions/countries will be followed in China.

In Korea, The clinical safety and vigilance reporting requirements are governed by the following MFDS's (The **M**inistry of **F**ood and **D**rug **S**afety) documents.

- MFDS Notification 2014-178 (Revised on Oct 31, 2014): Regulations for Approval of Clinical Trial Plan.
- Ministerial Decree No.1307 (Effective on Jul 29, 2016): Enforcement Regulations of the Medical Device Act including KGCP
- MFDS Notification No.2016-2 (Revised on Jan 14, 2016: Regulations on - Management of Medical Device Safety Information, Including Adverse Event Report.

E.9.1 *Adverse Events and Device Deficiencies*

E.9.1.1 Definition/classification

For the purposes of the clinical report, each AE will be classified according to ISO 14155:2011 definitions and are provided in table 4.

Where the definition indicates "device", it refers to any device used in the study. This might be the device under investigation, or any market released component of the system.

Table 5: Adverse Events Definitions

ISO Definitions for Clinical Investigations of Medical Devices for Human Subjects
Adverse Event (AE): *(ISO14155:2011 3.2)* Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, 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. *For Korea: Under KGCP Article 2 item 12, this definition is equivalent to the definition of Adverse Event*
Adverse Device Effect (ADE): *(ISO14155:2011 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 *For Korea: Under KGCP Article 2 item 13, this definition is equivalent to the definition of Adverse Device Effects.*
Unexpected Adverse Device Effects (UADE): *(applicable for Korea only: KGCP Article 2 item 15)* Adverse device effects showing differences in degree or severity from medical device-related information, including Investigator's Brochure or attached documents to medical devices
Serious Adverse Event (SAE): *(ISO 14155:2011 3.37)*

An 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 foetal distress, foetal 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.

For Korea: Under KGCP Article 2 item 14, this definition is equivalent to the definition of Serious AE or ADE.

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.

For Korea: Under KGCP Article 2 item 14, this definition is equivalent to the definition of Serious AE or ADE.

Unanticipated Serious Adverse Device Effect (USADE): *(ISO 14155:2011 3.42)*

Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report

NOTE: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.

Device deficiency: *(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 labelling.

Unavoidable AE

An Adverse Event inherent to a surgical procedure that is expected to occur in all subjects for a projected duration.

Event Description	Timeframe (hours) from the Surgical Procedure
Anesthesia related nausea / vomiting	24
Low-grade fever (<100°F or 37.8°C)	48
Sleep problems (insomnia)	72

In all geographies unavoidable AEs need not be reported unless the AE worsens or is present outside the stated timeframe post-implant. An event is not considered an AE if it has been identified as a pre-existing condition, unless the AE worsens or is present outside the stated post-Surgical Procedure timeframe.

In addition, further classification of the relationship will be done by the investigator according to the following parameters:

- **Device related:**

Events specifically related to the Devices (please see definition of AEs and Device Deficiency in Section E.9.1) including but not necessarily limited to insertion device breakage, insertion device dysfunction, cage movement-

migration, subsidence, screw breakage, screw pullout, screw dislodgement, rod breakage and inflammatory/allergic reaction to the Devices.

• **MAST™ Approach/Procedure related:**

Events specifically related to the minimally invasive surgical approach procedure including the minimally invasive access approach, decompression, and insertion of instrumentation. These events include but are not limited to local, temporary back pain caused by ligament distraction, dural tears, nerve root injury and bone fracture.

• **General Surgery related or Lumbar Fusion procedure related:**

Events related to general surgery in general who are not related to the MAST related events. These events could include but are not limited to, hematoma, wound pain, wound breakdown and infection.

• **Related to the disease:**

AEs related to the progression of degenerative lumbar spine. These events include but are not limited to recurrence of symptoms due to further degeneration of a previously healthy level leading to symptoms occurrence.

AE not related to diseases should be collected as well.

The above relationship parameters will be assessed and categorized as per the MEDDEV 2.7/3 levels of causality:

1) Not related: relationship to the device or procedures can be excluded when:
   - the event is not a known side effect of the product category the device belongs to or of similar devices and procedures;
   - the event has no temporal relationship with the use of the investigational device or the procedures;
   - the serious event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible;
   - the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible – and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious event;
   - the event involves a body-site or an organ not expected to be affected by the device or procedure;
   - the serious event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors);
   - the event does not depend on a false result given by the investigational device used for diagnosis, when applicable;
   - harms to the subject are not clearly due to use error;
   - In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.
2) Unlikely: the relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.
3) Possible the relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases were relatedness cannot be assessed or no information has been obtained should also be classified as possible.
4) Probable the relationship with the use of the investigational device seems relevant and/or the event cannot reasonably explained by another cause, but additional information may be obtained.
5) Causal relationship: the serious event is associated with the investigational device or with procedures beyond reasonable doubt when:
   - the event is a known side effect of the product category the device belongs to or of similar devices and procedures;

- the event has a temporal relationship with investigational device use/application or procedures;
- the event involves a body-site or organ that
    - the investigational device or procedures are applied to;
    - the investigational device or procedures have an effect on;
- the serious event follows a known response pattern to the medical device (if the response pattern is previously known);
- the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious event (when clinically feasible);
- other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out;
- harm to the subject is due to error in use;
- the event depends on a false result given by the investigational device used for diagnosis when applicable;
- In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

E.9.1.2 Recording and reporting of Adverse Events

In this study all AEs will be collected. The AE information will be collected throughout the study and reported to Medtronic on an electronic AE Form in the eCRF, one for each AE. See the AE eCRF for the information to be reported for each AE.

For AEs that require immediate reporting (see Table 5: Adverse Event reporting requirements), initial reporting shall be done by completing the appropriate eCRF. If the eCRF is not available reporting may be done by phone or e-mail (see section E.9.3 AE/DD reporting in case eCRF cannot be accessed and/or emergency contact details).

In case the investigator requires information from the sponsor in an emergency situation, the investigator can contact the Medtronic contacts available in the Investigator Site file. Contact details of the Study Team members are also given in section E.9.3 AE/DD reporting in case eCRF cannot be accessed and/or emergency contact details

The preferred way of transmission AEs and DDs is the Oracle Clinical (eCRF) system, but in case the eCRF cannot be accessed, the investigator can contact the below mentioned Medtronic personnel (preferably per email). Contact details available in the Investigator Site file:

a. Your local clinical contact person (monitor)
b. Clinical Study Manager
c. Clinical Safety Specialist

In case email is used to inform the Medtronic personnel, the AE / DD worksheet that can be found in the patient binders may be used for completion of available information, preferably signed by investigators and attached to the email.

The same CIP reporting timelines apply for all types of reporting as if the eCRF would be available.

E.9.1.3 Recording and reporting of Device Deficiencies

Device Deficiency information will be collected throughout the study and reported to Medtronic. Device Deficiencies that did not lead to an AE should be reported on a Device Deficiency Form in the eCRF, one for each Device Deficiency.

See the Device Deficiency eCRF for the information to be reported for each Device Deficiency that did not lead to an AE.

Device deficiencies that did not lead to an AE but could have led to an SADE
a) if either suitable action had not been taken,
b) if intervention had not been made, or
c) if circumstances had been less fortunate,

require immediate reporting (see Table 5: Adverse Event reporting requirements). Initial reporting shall be done by completing the appropriate eCRF. If the eCRF is not available reporting may be done by phone or e-mail *(*see section E.9.3 AE/DD reporting in case eCRF cannot be accessed and/or emergency contact details).

E.9.1.4 Adverse Event and Device Deficiency review process

All AEs and Device Deficiencies will be reviewed by the Medtronic Safety Representative. This review will include the determination whether the AE/Device Deficiency meets regulatory reporting requirements (see Table 5: Adverse Event reporting requirements). The sponsor will ensure timely AE/Device Deficiency reporting to meet global regulatory requirements.

A list of anticipated AEs that may be expected in nature can be found in the IFU of the used devices.

Table 6: Adverse Event reporting requirements

AE reporting requirements	
Serious Adverse Device Effects (SADE), including Unanticipated Serious Adverse Device Effect (USADE):	
Investigator submit to:	
Medtronic	Immediately (within 3 calendar days) after the investigator first learns of the event or of new information in relation with an already reported event.
Regulatory Authority	As per local reporting requirement.
EC/IRB	**Korea:** SADEs and USADEs causing death or life threatening must be reported within 7 calendar days from the date when the investigator had relevant effects reported or informed. In this case, the investigator shall make a detailed report of the SADEs, USADEs causing death or life threatening within 8 calendar days from the initial report. SADEs and USADEs excluding death or life threatening must be reported within 15 calendar days from the date when the investigator had relevant effects reported or informed. *(KGCP Article 8 item 18)* **All other geographies:** Submit to EC/IRB per local reporting requirement.
Sponsor submit to:	
Regulatory Authorities	**Korea:** SADEs and USADEs causing death or life threatening (including any oversea events) must be reported by the Korea Quality Team to the Medical Device Safety Bureay at MFDS within seven (7) calendar days from the date when the sponsor had relevant effects reported or

	informed. In this case, the sponsor shall make a detailed report of the SADEs, USADEs causing death or life threatening within eight (8) calendar days from the initial report. Other SADEs and USADEs excluding death or life threatening (including any oversea events) must be reported within fifteen (15) calendar days from the date when the sponsor had relevant effects reported or informed. *(KGCP Article 8 item 18)* **All other geographies:** Reporting timeframe as per local requirement.
EC/IRB	**Korea:** SADEs and USADEs causing death or life threatening (including any oversea events) must be reported by the Korea Quality Team to the IRB* and investigators within seven (7) calendar days from the date when the sponsor had relevant effects reported or informed. In this case, the sponsor shall make a detailed report of the SADEs, USADEs causing death or life threatening within eight (8) calendar days from the initial report. Other SADEs and USADEs excluding death or life threatening (including any oversea events) must be reported within fifteen (15) calendar days from the date when the sponsor had relevant effects reported or informed. *(KGCP Article 8 item 18)* ** The reporting to the IRB is applicable only if the PI failed to report to the IRB, or what was reported by the PI needs to be changed.* **All other geographies:** Submit to EC/IRB per local reporting requirement.
Serious Adverse Events (SAE)	
Investigator submit to:	
Medtronic	**Korea:** The PI shall quickly report all SAEs **(**excluding what is classified in the protocol as ones not requiring immediate reporting) as expedited reports of adverse device effects under Attached Form No. 35 to the sponsor within the period provided in the protocol. *(KGCP Article 7 item 11)* It is recommended for the investigator to report safety events as soon as possible but no longer than 15 calendar days. **Mexico:** Investigators must inform the study monitor/sponsor on the same day as they have knowledge of the event. **All other geographies:** Immediately (within 3 calendar days) after the investigator first learns of the event or of new information in relation with an already reported event.
Regulatory Authority	As per local reporting requirement.
EC/IRB	Submit to EC/IRB per local reporting requirement.
Sponsor submit to:	
Regulatory Authorities	Reporting timeframe as per local requirement.
EC/IRB	Submit to EC/IRB per local reporting requirement.

Adverse Device Effects (ADE)	
Investigator submit to:	
Medtronic	Immediately (within 3 calendar days) after the investigator first learns of the event).
Regulatory Authority	As per local reporting requirement.
EC/IRB	Submit to EC/IRB per local reporting requirement.
Sponsor submit to:	
Regulatory Authorities	Reporting timeframe as per local requirement
EC/IRB	Submit to EC/IRB per local reporting requirement.
All other AEs	
Investigator submit to:	
Medtronic	Submit (within 20 calendar days) after the investigator first learns of the event.
Regulatory Authority	As per local reporting requirement.
EC/IRB	Submit to EC/IRB per local reporting requirement.
Device Deficiencies with SADE potential	
Investigator submit to:	
Medtronic	Mexico: Investigators must inform the study monitor/sponsor on the same day as they have knowledge of the event. All other geographies: Immediately (within 3 calendar days) after the investigator first learns of the deficiency or of new information in relation with an already reported deficiency.
Regulatory Authority	As per local reporting requirement.
EC/IRB	Submit to EC/IRB per local reporting requirement.
Sponsor submit to:	
Regulatory Authorities	Reporting timeframe as per local requirement
EC/IRB	Submit to EC/IRB per local reporting requirement.
All other Device Deficiencies	
Investigator submit to:	
Medtronic	Submit (within 20 calendar days) after the investigator first learns of the deficiency.

Regulatory Authority	As per local reporting requirement.
EC/IRB	Submit to EC/IRB per local reporting requirement.

Refer to APAC addendum for reporting in APAC region.

E.9.1.5 Reporting of product complaints

Product Complaint: Any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness or performance of a medical device that has been placed on the market.

All devices used in this study are market released. Therefore, vigilance and Medical Device Reporting (MDR) reporting is applicable and AEs related to any market-released device during the study must be reported. The reporting of product complaints is not part of the clinical study and should be done in addition to the Adverse Event reporting requirements. Refer to local regulations for reporting requirements.

It is the responsibility of the investigator to report all product complaint(s) associated with a medical device distributed by Medtronic, regardless whether they are related to intended use, misuse or abuse of the product. Reporting must be done immediately and via the regular channels for market-released products..

In case the AE is related to a non-Medtronic market released device used during the study, post market surveillance is also applicable and the investigator is responsible for immediate reporting of the product complaint via the regular channels for market released products.

Medtronic will notify the regulatory authorities (e.g. Competent Authority) if a complaint meets the criteria of AE reporting according to local requirements. Besides the data on the Case Report Forms, imaging data from MRI, CTs , X-Rays and/or medical records may also be collected for additional assessment.

E.9.2 *Adverse Event Advisory Committee*

No AEAC committee will be installed for this PMR study.

E.9.3 *AE/DD reporting in case eCRF cannot be accessed and/or emergency contact details*

The preferred way of transmission AEs and DDs is the Oracle Clinical (eCRF) system, but in case the eCRF cannot be accessed, the investigator can contact the below mentioned Medtronic personnel (preferably per email). Contact details available in the Investigator Site file:

a. Your local clinical contact person (monitor)
b. Clinical Study Manager
c. Clinical Safety Specialist

In case email is used to inform the Medtronic personnel, the AE / DD worksheet that can be found in the patient binders may be used for completion of available information, preferably signed by investigators and attached to the email.

The same CIP reporting timelines apply for all types of reporting as if the eCRF would be available.

E.10 Subject accountability

Patients may withdraw from the study at any time and for any reason. Stop of data collection for patients in the study may occur in the following cases:

- Withdrawal of consent by patient
- Patient lost-to-follow-up
- Patient death
- Patient did not undergo the instrumented lumbar fusion as defined in this protocol

If a patient is withdrawn from the study, the reason for withdrawal shall be recorded in the eCRF and in the subject's hospital record. Subjects withdrawn from the study will only be replaced when patients did not undergo the instrumented lumbar interbody fusion with posterior fixation as defined in this protocol and if the enrollment is still open. In that case only, these patients will not contribute to the site and region specific enrollment limits nor to the maximum amount of patient enrollments per procedure.

Compliance to the minimum recommended follow-up schedule is essential to enable the analysis of the results in a scientifically sound and meaningful way. If, for whatever reason, the patient follow-up cannot be scheduled within the time window or occurred outside the time window, it is still essential to schedule a follow-up visit and to document the patient data at a date as close as possible to the calculated follow-up date.

Patients that are lost-to-follow-up should be avoided as much as possible and investigators are urged to do their utmost best to maintain patient's follow-up compliance as per CIP.

Withdrawal of consent:

Subjects may withdraw from the study at any time and for any reason. If a subject withdraws from the study, the Investigator will document the reason for withdrawal, if given by the subject, in the source documents and in the subject's CRF. Subjects withdrawn from the study will not be replaced. The follow up of these subjects will be according to the standard of care at the site.

Lost to follow up:

Before considering a patient as lost to follow up, the Investigator should make any attempt to contact the subject (or relevant other persons associated with the subject) to have the subject return for follow-up to determine their clinical status and the occurrence/resolution of AEs, if any.

Before documenting a subject as lost to follow up, the Investigator should document in the CRF and source documents at least 3 contact attempts with the subject, subject's relatives or other persons associated with the subject. In addition, the investigator should make a reasonable effort to ascertain the reason(s), while fully respecting the subject's rights (e.g. if a patient is deceased, the date of death should be completed or if the subject is alive, the date of last contact with patient should be provided).

E.11 Study deviations and CIP changes

A study deviation is an event where the investigator or site personnel did not conduct the clinical study according to the Clinical Investigational Plan or Clinical Investigation Agreement. The investigator is not allowed to deviate from the above mentioned documents except under emergency circumstances to protect the rights, safety and well-being of human subjects. All deviations shall be documented and explained, regardless the reason for the deviation.

In this post market release study with a prospective design Deviations are defined as deviations related to:

- Data Release or Patient Informed Consent procedure
- Enrolled patient does not meet Inclusion/Exclusion criteria
- Visit not done
- Assessment(s) at the visit not performed
- Visit outside the CIP defined visit window
- Patient did not undergo the instrumented lumbar fusion as defined in this protocol
- Improper SAE / ADE / SADE reporting (please see section Table 5 AEs of this CIP).
    - Any (U)(S)A(D)Es, Device Deficiencies with SADE potential and Serious Procedure related AEs, that are not reported timely
    - Any AE or device deficiency without (S)A(D)E potential that is not reported with 20 calendar days
- EC/IRB approval not obtained, if required

All deviations shall be recorded in the eCRF and those below require immediate actions to be taken in case of their occurrence:

Table 7 Deviation - Actions overview table

Deviation:	**Action:**
No Patient Data Release (or Informed Consent) form properly obtained before enrollment	Stop data entry and take all necessary actions in order to obtain the document; if not obtained, data will not be analyzed. Complete the protocol deviation form in the CRF
Enrolled patient does not meet Inclusion/Exclusion criteria	Evaluate in-and exclusion criteria of study to prevent deviation from reoccurring. Complete the protocol deviation form in the CRF
Visit not done	Complete the protocol deviation form in the CRF
Assessment(s) at the visit not performed	Complete the protocol deviation form in the CRF
Visit outside the CIP defined visit window	Complete the protocol deviation form in the CRF
Improper SAE / ADE / SADE reporting	Report the event immediately according to Section **E.9 Adverse events** of this CIP. Complete the protocol deviation form in the CRF
EC/IRB approval not obtained, if required	Do not enroll (or stop patient enrolment) and take all necessary actions in order to obtain the EC/IRB approval. Complete the protocol deviation form in the CRF
Patient did not undergo the instrumented lumbar fusion as defined in this protocol	Refer to section (E.10 Subject accountability) Complete the protocol deviation form in the CRF

Medtronic will assess the significance of all deviations and evaluate the need to amend the Clinical Investigation Plan, to early terminate the investigation or site termination in case the deviations only relate to one site, in accordance with Medtronic SOPs.

E.11.1 *Request for approval of study deviations*

This is a study conducted within the IFU of the used Devices and due to the nature of the Protocol Deviations as defined in the section above pre-approval for study deviations will not be applied in this post market release study.

In any situation during the conduct of this study the investigator shall exercise his/her judgment to always safeguard the subject's interest independent whether the action to be taken will lead to a Protocol Deviation or not. The investigator shall report the deviation as soon as possible to Medtronic and the reviewing EC/IRB, if applicable. Medtronic will inform the regulatory authorities, if required.

E.11.2 *Reporting requirements for study deviations*

The investigator shall adhere to EC/IRB requirements and procedures for reporting study deviations.

Medtronic is responsible for analyzing deviations, assessing their significance, and identifying any additional corrective and/or preventive actions (e.g. amend the CIP, additional training, terminate the study, etc.). Repetitive or serious investigator compliance issues may result in the need to initiate a corrective action plan, and in some cases freeze enrollment or ultimately terminate the investigator's participation in the clinical study. Medtronic will provide investigation site-specific reports to the investigators on a yearly basis summarizing information on deviations that occurred at the investigational site.

E.11.3 Amendments to the Clinical Investigation Plan

The investigator will propose any appropriate modification(s) of the Clinical Investigation Plan or investigational device or investigational device use. Medtronic will review this proposal and decide whether the modification(s) will be implemented.

Medtronic will submit any significant amendment to the Clinical Investigation Plan, including a justification for this amendment, to the appropriate regulatory authorities and to the investigators to obtain approval from their EC/IRB, if applicable. Administrative amendments to the Clinical Investigation Plan will be submitted to the EC/IRB and appropriate regulatory authorities for notification, if applicable.

F QUALITY CONTROL PROCEDURES

F.1 Procedures for database management

F.1.1 *Data collection*

The investigator must ensure accuracy, completeness and timeliness of the data reported in the CRFs and in all other required reports. Data reported on the CRFs which are derived from source documents must be consistent with the source documents and discrepancies need to be justified in the CRF.

Only authorized persons can complete CRFs. CRFs shall be signed by investigators (physicians only) as specified on the Delegated Tasks List included in the Investigator Site File.

The Electronic Data Capture (EDC) system maintains an audit trail on entries, changes or corrections in CRFs. If a person is only authorized to complete CRFs or make changes to an already signed CRF, the investigator shall re-sign this CRF.

Besides the data on the Case Report Forms, imaging data from MRI, CTs, X-Rays may also be collected for assessment by a qualified evaluator.

F.1.2 *Source data to be directly recorded on the Case Report Forms*

The following data will be recorded directly on the CRF and is considered as source data:

- Patient work status and rehabilitation program information
- Patient neurological status

In case data are collected additionally to CRF data such as the CT scan, these will be handled as source data.

F.1.3 *Time windows for completion and submission of Case Report Forms*

Data collected on each patient will be recorded on a web-based electronic Case Report Form (eCRF).

As a guideline the eCRFs should be up-dated preferably within 20 working days after the data are available. Different timelines for AE reporting apply and are described in Table 5: Adverse Event reporting requirements.

Instructions for proper completion of the CRF and how the web-based system should be used will be provided to the clinical site at the start of the study.

F.1.4 *Data review and processing*

Data management will be done according to Medtronic SOPs and the Data Management Plan for this clinical study. These documents will be made available on request.

All collected data will be reviewed for completeness, correctness and consistency. In case of issues, queries will be sent to the investigator to complete, correct or comment the data.

Data stored electronically shall be maintained in accordance to Medtronic corporate policies and record retention schedule.

F.2 Monitoring procedures

Monitoring visits will be conducted at the start, during and at the closure of the clinical study in accordance with Medtronic SOPs and the Monitoring Plan.

Trained Medtronic personnel or delegates appointed by Medtronic may perform study monitoring at the study site in order to ensure that the study is conducted in accordance with the CIP, the Clinical Trial Agreement, and applicable regulatory and local requirements. Medtronic, or delegates, must therefore be allowed access to the subjects' case histories (clinic and hospital records, and other source data/documentation) upon request as per the Patient Informed Consent/Data Release Form Research Authorization (where applicable) and Clinical Trial Agreement.

F.2.1 *Site Initiation Visits*

Site Initiation Visits will be conducted for sites participating in this trial to ensure that protocol-related activities are conducted in compliance with this CIP. Site Initiation Visit activities may be performed on site or remotely, at the discretion of the Clinical Study Manager.

F.2.2 *Interim Monitoring Visits*

During the interim monitoring visits it will be verified whether signed and dated Informed Consent Forms / Data Release Forms have been obtained from each subject before any clinical-study-related procedures are undertaken.

For this study a risk-based monitoring will be applied. Frequency of monitoring visits, detailed in a separate monitoring plan, will occur based on subject enrollment, timing of subject follow up visits, number of subjects with completed follow-up visits, volume of eCRF, numbers of AEs and study deviations, duration of the study, study compliance, remote monitoring findings, findings from the previous monitoring visit and any suspected inconsistency in data that requires investigation or other relevant reason(s). The level of monitoring will be defined in the monitoring plan.

Monitoring will be conducted to monitor compliance with the protocol and adherence to the data collection procedures, to assess the accuracy and completeness of submitted clinical data and to verify that records and documents are being properly maintained for the duration of the study. In case of an on-site monitoring visit, the monitor will perform source data verification by review of original patient documents.

When source data verification is performed, the monitor must have direct access to original source documentation, certified copies of the original source must be provided, or supervised access in situations wheredirect access is not possible.

If electronic source documentation is used at the site, the site must provide to the monitor:

1. Direct access to the electronic medical record(s), or direct access to the electronic medical record(s) by reviewing alongside appropriate study staff

2. Certified copies of the electronic medical record

A certified copy is a copy of original source documents or printout of original electronic source documents generated or produced by the clinical research site. It requires to be verified (as indicated by a dated signature of a member of the investigation site team with a statement that it is a true reproduction of the original source document) or generated through a site's validated process. It is possible to combine multiple pages (which were copied or printed) together and sign and date the top page with a comment that this is a true and complete reproduction of the original source documents.

The monitor must verify that he/she has complete access to all original or certified copies of source documentation required for the study.

F.2.3 *Close out visits (COV)*

Close Out phone call or on-site visits will be conducted for sites participating in this trial to ensure that protocol-related activities are conducted in compliance with this CIP.

The Investigator Site file will be reviewed for completeness however verification of individual regulatory documents may also be confirmed if noted in prior monitoring visits reports and do not necessarily need to be re-reviewed during the Close-out Visit.

Site Close out Visits may be performed on site or remotely, at the discretion of the Clinical Study Manager. The minimum activities required for the COV remain the same whether performed remotely or by visiting the site and will be documented on the Site Close Out report.

It is expected that all sites will have a close-out visit; however, in rare cases where it is not reasonable or possible for a COV to occur, it is at the discretion of the Clinical Study Team designee and the Monitoring Manager to omit the closeout visit. The decision and rationale for omitting the visit should be documented by the Clinical Study Team designee, and the documentation should be filed in the Investigator's file and the sponsor's File.

COV activities may be performed for individual trial sites prior to closure of the entire trial.

F.2.4 *Accessibility of investigation site staff and study materials*

The principal investigator(s), his/her delegate(s) and the study coordinator(s) shall be accessible to Medtronic field personnel and the Clinical Study Manager. This accessibility is of particular importance for reviewing data in the Case Report Form (CRF). Direct access to patient medical files for source data verification (if applicable) will need to be granted and prepared prior to any monitoring visits.

F.2.5 *Audits and investigation site inspections*

In addition to regular monitoring visits, Medtronic may conduct audits at participating investigation sites. The purpose of an audit is to verify the adequate performance of the clinical study related activities. Independent of the employees involved in the clinical study, regulatory authorities may also perform inspections at participating investigation sites. Any regulatory authority inspection announcements shall be forwarded immediately to the Clinical Study Manager.

The investigator and/or institution shall permit Medtronic and regulatory bodies direct access to source data and documents, taking into account any restrictions due to local law, to perform clinical study-related monitoring, audits, EC/IRB review (if applicable), and regulatory inspections.

F.3 Study suspension or early termination

F.3.1 *Early study suspension or termination*

Medtronic or Regulatory Authority may decide to suspend or prematurely terminate the clinical study if interim analysis indicates that the results significantly differ from the clinical study objectives. If the clinical study is terminated prematurely or suspended, Medtronic shall promptly inform the clinical investigators of the termination or suspension and the reason(s) for this. The investigator shall then promptly inform the reviewing EC/IRB, if required and the study patients.

F.3.2 *Early investigation site suspension or termination*

Medtronic, EC/IRB or Regulatory Authority may decide to suspend or prematurely terminate an investigation site (e.g. in case of expiring approval of the reviewing EC/IRB, non-compliance to the Clinical Investigation Plan or lack of enrollment). If an investigation site is suspended or prematurely terminated, Medtronic shall promptly inform the investigator(s) of the termination or suspension and the reason(s) for this. The investigator shall then promptly inform the reviewing EC/IRB, if required and the study subjects or their legal representative.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definite outcomes, investigators must assess whether to continue, modify or immediately stop the clinical study in the respective investigation site and immediately inform the sponsor and EC/IRB, if applicable.

F.3.3 *Subject follow-up in case of termination*

In case of early termination of the study, the patients will continue to be followed according to the routine practice of the site.

F.4 Study close out

In case of close out the investigators will be notified and notification/report to EC/IRB and Regulatory Authority will be done, if required per local regulations.

G DATA ANALYSIS AND REPORTING

G.1 Analysis of clinical data

For the purpose of the analysis, all subjects who are enrolled and undergo a minimally invasive lumbar fusion procedure will be included in the analyses. All the analyses will be based on observed data. No missing data will be imputed.

G.1.1 *Analysis of Primary Endpoint*

To evaluate whether the primary endpoint improvement in ODI at 3 months is equivalent for the spondylolisthesis DDD subjects treated with anterolateral approaches and the ones treated with posterior approaches, the two-sided 95% confidence interval for the mean difference of ODI improvement at 3 months will be calculated. If the 95% CI is within the equivalent range of (-10, 10), then the primary objective is met. In addition, the paired t-test will be carried out for each group to see whether the ODI improvement at 3 months from baseline is significant.

G.1.2 *Analysis of Secondary Endpoints*

For the first secondary objective, the similar method as the one outlined above for the primary endpoint will be used to assess whether the ODI improvement at 3 months is equivalent for the non-spondylolisthesis DDD subjects treated with anterolateral approaches and the ones treated with posterior approaches.

For secondary points ODI improvement at other follow-ups other than at 3-months visit; change of VAS back and leg pain intensity and EQ-5D at all follow-ups through 5-year visit, summary statistics will be provided and the paired t-test will be used to test whether the improvement at each follow-up from baseline is significant.

The neurological success rate will be summarized at each follow-up. Overall neurological success will be defined as maintenance or improvement in all sections (motor, sensory, reflex, and straight leg raising) for the time period evaluated. In order for a section to be considered a success, each element in the section must remain the same or improve from the time of the baseline evaluation to the time period evaluated. Therefore, if any one element in any section does not stay the same or improve, then a patient will not be considered a success for neurological status.

Time-to-event-analysis will be conducted for fusion success. The fusion success rate will be summarized for 1, 2, 3, 4, 5 -year follow-up, if applicable. If a subject shows fusion success at early timepoints and non-fusion at a later timepoint, the fusion status at all earlier time points should be considered as non-fusion.

For 2-level subjects, fusion success will be defined as achieving fusion at both treated levels.

For secondary surgery at index levels, secondary surgery at adjacent levels and AEs, survival analysis will be performed to estimate the cumulative event rate up to 5 years.

Healthcare utilization will be measured with the following three cost components:

(1) resources: procedure, length of hospital stay, additional medical visits (outpatient consultations, visits to primary care services, etc)

(2) medications and

(3) non-pharmacologic therapies: rehabilitation program

For time needed for first ambulation and surgery recovery day, summary statistics for continuous variable will be provided by subgroups.

The analyses for the primary endpoint and secondary endpoints outlined in secondary objectives 2 and 3 will be done for all subjects and the following subgroups:

1) In DDD patients with spondylolisthesis with stenosis
2) In DDD patients with spondylolisthesis but without stenosis
3) In DDD patients with stenosis but without spondylolisthesis
4) All patients not included in subgroup 1), 2), 3).

G.1.3 *Additional Data Analysis*

For other measurements, continuous variables will be summarized using mean, standard deviation, median, minimum and maximum while the categorical variables will be summarized using frequency and percentage.

Baseline information will be summarized for all DDD patients and by subgroups as outlined below and/or per surgical procedure (ALIF, OLIF, DLIF, PLIF, TLIF, MIDLF).

1) In DDD patients with spondylolisthesis and stenosis
2) In DDD patients with spondylolisthesis without stenosis
3) In DDD patients with stenosis without spondylolisthesis
4) All patients not included in subgroup 1), 2), 3).

Determining if there is a correlation between sagittal balance at baseline and the radiological findings and the clinical outcomes at the follow-up visit, in those sites where this assessment is standard of care.

Several subgroup analyses will be conducted based on DN4 scores (respectively for leg DN4 score and back DN4 score) at baseline, 3 months and 12-month visit. For subjects with baseline DN4 ≥ 4, the number and percentage of subjects with DN4 ≥ 4 or < 4 at 3 months and 12 months follow-up will be calculated and presented. Similarly for subjects with baseline DN4 < 4, the number and percentage of subjects with DN4 ≥ 4 or < 4 at 3 months and 12 months follow-up will be calculated and presented.

In addition, ODI, EQ5D, VAS back and leg pain score at baseline, at each follow-up and the improvement of each variable from baseline at each follow-up will be presented by the subgroups defined by baseline DN4 scores and/or DN4 scores at follow-ups. Statistical comparison may be carried out for these subgroups.

More subgroups analyses may be conducted as exploratory analyses by taking into consideration of pathology and surgical approach perspective.

Any deviation(s) from the original statistical plan will be documented with a justification.

G.1.4 *Interim Analysis*

In addition to a final statistical analysis, an interim analysis will be conducted when all subjects reached 3-month visit. At that time, the 3-month data including the primary endpoint improvement of ODI at 3-month visit from baseline will be finalized and the conclusion for the primary endpoint will remain unchanged at the final analysis.

G.2 Publication Policy

Publications and presentations referring to this clinical study will be coordinated by Medtronic to allow the use of all available data. The corporate publication policy will have to be adhered to by all participating investigation sites.

Medtronic intends to submit the results of the clinical study in a scientific journal. In addition to the primary publication, interim reports could be prepared according to the publication plan.

Authorship selection for publications using multi-center data will be determined based on the International Committee of Medical Journal Editors (ICMJE) published guidelines (JAMA 2013) and according to the criteria defined in the publication plan.

In addition to the ICMJE guidelines, an author algorithm will be developed by Medtronic Spinal and Biologics (MSB) and approved by the Publication Committee. The algorithm will be used as a base to determine authorship for publications. This investigator credit system will focus on the enrollments and implants in total, but also includes data quality and active participation during the publication development.

Due to the multicenter design of the study, one investigator per participating study site can be named as author or can be acknowledged in the paper.

The number of authors will be dependent on the regulations of the target journal. Names of all participating principal investigators will appear in the Acknowledgement section of the publication.

Subject to prior approval by the Advisory Committee:

- Investigation site may access and use the data provided by itself for scientific publications
- Pooling data from several investigation sites for publication purposes, national projects and international projects

Medtronic as the owner of the data can use the data and/or any results derived from the data or publications based on that data for marketing purposes, further research and development of devices or educational use.

The study sponsor will collect data in such way that no subject can be identified, and monitor study records.

Furthermore, the study is registered in a public database, on ClinicalTrials.Gov with the following identifier: NCT02617563.

H MANAGEMENT

H.1 Study staff

A separate list with the study contacts and study monitors will be filed in the sponsor's Project Files and the Investigator Site Files. The sponsor will keep this list up to date.

H.2 Advisory committees

H.2.1 *Advisory Committee*

During the start-up phase of the study, the MASTERS-D 2 Advisory Committee was established to perform one or more of the following:

- To review the Clinical Study Protocol, and give feedback to Medtronic concerning the study design and scientific value of data collection;
- To safeguard the interests of clinical study participants and monitoring the overall conduct and progress of the clinical study,
- To evaluate the scientific validity and guide the development and timing of the publications and congress presentations (publication strategy), ensure compliance to ICMJE guidelines and Medtronic policy on publications. The members of the advisory committee are listed in the Appendix K.1.

If needed, additional representatives and experts could be invited to support the activities of the MASTERS-D 2 Advisory Committee.

Reference is made to the MASTERS-D 2 Advisory committee Charter which is available upon request.

H.2.2 *Data Monitoring Committee*

No Data Monitoring Committee will be installed for this clinical study as no interventions intended to prolong life or reduce risk of a major adverse health outcome (e.g., cardiovascular events) are evaluated, for which favorable or unfavorable study results suggest study termination. Nor are there safety concerns suggesting the need for a Data Monitoring Committee.

H.2.3 *Publication Committee*

The advisory committee will perform publication committee duties. This committee will develop a final publication plan according to Medtronic Standard Operating Procedures. The publication plan will be defined during the course of the study and may be amended by the PC if additional conferences and journals are deemed appropriate.

H.3 Records and reports

H.3.1 *Investigator records*

At a minimum, the following records must be kept by the investigator:

- Clinical Investigation Plan and, if applicable, any amendments
- Medtronic and EC/IRB approved Patient Informed Consent/Data Release form
- Regulatory Authority approval or notification, if applicable

- Fully signed clinical investigation agreement and confidentiality agreement (if not included in the clinical investigation agreement)
- Completed Delegated Task List and Curriculum Vitae of all investigation site personnel (if applicable)
- Training documentation of all investigation site personnel
- Relevant communications
- Subject screening log and/or subject identification log
- Signed, dated and fully executed informed consent forms
- Fully executed CRFs and corrections
- Any other records that local regulatory agencies require to be maintained.

H.3.2 *Investigator reporting responsibilities*

The investigator is responsible for the preparation and submission to the sponsor of all electronic case report forms (eCRFs). If any action is taken by an EC/IRB with respect to the study, the information must be forwarded to Medtronic.

Table 8: Investigator Reporting Responsibilities Overview

Report	Submit to	Description
Premature termination or suspension of the study	Medtronic and EC/IRB	Provide prompt notification of termination or suspension and reason, in accordance with local regulations
Study enrollment complete	EC/IRB	Provide notification that enrollment is completed, in accordance with local regulations
Protocol Deviation	Medtronic	Complete the Protocol Deviations Forms in the eCRF
Adverse events	Medtronic	Report according to reporting timelines provided in Table 5
Final Report in accordance with local regulations	EC/IRB	Submit final report in accordance with local regulations.

H.3.3 *Sponsor records*

At a minimum, the sponsor will keep the following records:

- All essential study documents and correspondence that pertains to the clinical study
- CIP and, if applicable, any amendments
- Instructions for Use
- Curriculum vitae of investigators and site staff
- Delegated Task Lists and training records of investigators and site staff
- EC/IRB approvals/notifications and regulatory approvals/notifications, if applicable
- Signed Clinical Investigation Agreements and signed agreements with third parties
- Shipping records for clinical-investigation related documents and materials
- Medtronic and EC/IRC approved Patient Informed Consents/Data Release Forms

- Site selection reports, site initiation reports and monitoring visit reports
- Adverse event and Device Deficiency reports
- Fully executed CRFs and corrections

H.3.4 *Sponsor reporting responsibilities*

Below Table 8 summarizes the sponsor reporting responsibilities to the EC/IRB or Regulatory Authorities that approved this clinical study

Table 9: Sponsor Reporting Responsibilities Overview

Report	Submit to	Description
Adverse events	Investigators, Relevant Authorities and EC/IRB	Notification when appropriate (based upon perceived risk), and when required by relevant local authorities and EC/IRBs
Premature termination or suspension of the study	Investigators, Relevant Authorities and EC/IRB	Provide prompt notification of termination or suspension and reason, according to local regulations
Study enrollment complete	Investigators, Relevant Authorities and EC/IRB upon request	Medtronic will notify the investigators within 2 weeks of the completion of enrollment. Investigators will inform their EC/IRB, when required. Regulatory Authorities will be informed in accordance with local regulation.
Final report	Investigators, Relevant Authorities and EC/IRB upon request	Medtronic will provide all investigators with a copy of the final report of the study. Investigators will submit the final report to their EC/IRB, if required. Regulatory Authorities will be informed in accordance with local regulation.

H.3.5 *Record retention*

The investigator or the medical institution where the study was conducted must retain the Investigator Site File, patient medical files and CRFs in accordance with local law and regulations for a minimum period of 2 year (or longer if local laws require) after finalization of the clinical study report. In Europe, the documentation shall be kept for a period of at least 15 years after the clinical investigation with the device in question has ended.

The investigator or the medical institution where the study was conducted should take measures to prevent accidental or early destruction of the clinical study related materials.

H.4 Miscellaneous

H.4.1 *Insurance*

The sponsor is a wholly owned subsidiary of Medtronic , which as the parent company of such entity maintains appropriate clinical study liability insurance coverage as required under applicable laws and regulations and will comply with applicable law and custom concerning specific insurance coverage. If required according to local regulations, a Clinical Trial Insurance statement/certificate will be provided to the EC/IRB.

H.4.2 *Subject compensation and indemnification*

As per UK research governance framework, indemnity arrangements will be put in place prior to the start of the study. For the other participating countries, local regulations to post market study requirements will apply and standard indemnity agreement is in place.

H.4.3 *Subject confidentiality*

Subject confidentiality will be maintained throughout the clinical study to the extent permitted by law. That is, every attempt will be made to remove subject identifiers from clinical study documents. For this purpose, a unique subject identification code (site number and subject number) will be assigned and used to allow identification of all data reported for each subject. This will also ensure that the information can be tracked back to the source data.

The sponsor, Medtronic, will collect this key-coded data and monitor study records. Third parties e.g. auditors, EC/IRBs, Governmental regulatory authorities may also have access to the study records. Participating patients will not be identified by name in any published reports about this study.

I RISKS AND BENEFITS

I.1 Anticipated Clinical Benefits

Patients will be submitted to a single or double level instrumented fusion procedure using PLIF,TLIF, ALIF, OLIF, DLIF or MIDLF techniques via a minimally invasive procedure and will receive the same medical treatment as if they would not participate in this study.

Participation contributes to expand the knowledge base with respect to the minimally invasive procedures in a broad patient population.

I.2 Risks

The investigator must continuously monitor, assess and document the risks (Declaration of Helsinki 2013).

All devices used in this clinical study are released for distribution at the moment of clinical study start. Medtronic is not aware of any significant problems with this product. In the clinical study, the products will be used in accordance with their labeling; therefore no risks other than the risks typically associated with a routine device implantation and follow-ups are anticipated. Reference is made to the IFU for a detailed list of all risks associated with the devices.

In addition subjects are treated according to general clinical practice. No additional risks are associated with participation in this clinical study.

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K APPENDICES

K.1 Names and addresses

K.1.1 *List of contact persons*

Sponsor:

List of sponsor's staff will be kept separate from the CIP and provided to the investigators. The sponsor will maintain an updated list.

Advisory Committee Members

The MASTERS-D 2 Advisory Committee in the therapeutic area of the minimally invasive lumbar fusion techniques for treatment of the degenerative lumbar spine consists of scientific experts. The list will be kept separately from the CIP.

K.2 Case Report Forms

A copy of the CRF and amendments, if applicable, will be filed in the sponsor's Project Files and the Investigator Site Files.

K.3 Sample Investigator Agreement

A sample of the Investigator Agreement will be filed in the sponsor's Project Files.

K.4 Abbreviations

AE	Adverse Event
ADE	Adverse Device Effect
ALIF	Anterior Lumbar Interbody Fusion
APAC	Asia Pacific
ASD	Adjacent Segment Disease
BMI	Body Mass Index (kg/m2)
BRC	Bakken Research Center
CI	Confidence Interval
CIP	Clinical Investigation Plan ('Protocol')
CRF or e-CRF	Electronic (Web Based) Case Report Form
CT	Computer Tomography
CRO	Clinical Research Organization
DD	Device Deficiency
DDD	Degenerative Disc Disease
DLIF	Direct Lateral Interbody Fusion
DN4	Douleur Neuropathique 4 (neuropathic pain)
EC	Ethical Committee
EDC	Electronic Data Capture
FU	Follow-up
IFU	Instructions for Use
IRB	Institutional Review Board
LLIF	Lateral Lumbar Interbody Fusion

MAST™	Minimal Access Spinal Technologies
MIDLF	Midline Lumbar Interbody Fusion
MILIF	Minimally Invasive Lumbar Interbody Fusion
MRI	Magnetic Resonance Imaging
MIS	Minimally Invasive Surgery
ODI	Oswestry Disability Index
OLIF	Oblique Lumbar Interbody Fusion
DRF	Data Release Form
PIC	Patient Informed Consent
PLIF	Posterior Lumbar Interbody Fusion
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SDV	Source Data Verification
SOP	Standard operating procedure
TLIF	Transforaminal Lumbar Interbody Fusion
VAS	Visual Analogue Scale
XLIF	Extreme Lateral Interbody Fusion

K.5 Definitions

Table 10: Definitions

Open lumbar procedure :	Surgical technique using a midline approach and requiring a partial or complete detachment of the lumbar fascia and paraspinal muscles to address the spinal pathology and placement of instrumentation.
Minimally invasive procedure :	Muscle sparing surgical technique using an inter-muscle or trans-muscle splitting approach, minimizing detachment of the lumbar fascia and paraspinal muscles to address the spinal pathology and placement of instrumentation.
Definitions for **instrumentation** techniques :	
Mini-open technique :	Instrumentation placement using **direct vision of target structures** via an inter-muscle or trans-muscle splitting approach.
Percutaneous technique :	Instrumentation placement using radiographic or navigation guidance via stab incisions **without direct vision of target structures**.

K.6 Sample Statement that no Ethics Committee approval is required

MASTERS-D 2: A Prospective, 5-Year Global Study on MAST™ Minimally Invasive Fusion Procedures for the Treatment of the Degenerative Lumbar Spine.

The purpose of this global study is to collect, in a consistent manner, demographic data, implant information and clinical data of patients who are planned to be submitted to single or double level instrumented posterior lumbar interbody fusion using a minimally invasive procedure. Patients will receive via a minimally invasive approach the CD HORIZON® Spinal System which is the main set of devices to be used in this study and consists of a variety of shapes and sizes of rods, hooks and screws that has the function to help provide immobilization and stabilization of spinal segments as adjunct to fusion. All Devices within the scope of this study shall be used within its intended use as described in the approved manual and Instructions for Use for which Medtronic obtained regulatory market release (for example CE Marking in Europe).

Considering that the devices that will be used in this project have obtained regulatory market approval (e.g. CE Marking in Europe), and considering that for this study the patients will not necessitate any additional treatment other than the standard of care and will not expose patients to a higher risk, please check one as applicable:

☐ I declare that I have confirmed with my EC/IRB* that neither approval nor notification is required according to the local EC/IRB requirements for this project, and patient enrollment can start. This is in accordance with the country law on clinical research, and the hospital's regulations.

☐ I declare that the EC/IRB has been notified about this project, and that according to the local EC/IRB requirements, patient enrollment can start. This is in accordance with the country law on clinical research, and the hospital's regulations.

Name: _____

Signature: _____

Date: _____

Hospital: _____

*EC = Ethics Committee; IRB = Institutional Review Board;