The Sagittal Plane Shear Index (SPSI™) for planning whether to fuse after decompressing a stenotic lumbar level

Short Study Name: SPSI™ for planning lumbar spinal stenosis surgery

Protocol Reference: SPSI-01

Protocol Version: Version 02

Version Date: 18-October-2018

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PROTOCOL SIGNATURE PAGE

Title The Sagittal Plane Shear Index (SPSI™) for planning whether to fuse after decompressing a stenotic lumbar level

Protocol Reference: SPSI-01

Investigator's statement

I agree to conduct this clinical investigation in accordance with the design and specific provisions of this clinical investigation plan; modifications to the clinical investigation are acceptable only with a mutually agreed upon clinical investigation plan amendment as approved by the Sponsor and applicable Ethics Committees. I agree to await Ethics Committee approval of the clinical investigation plan and informed consent before initiating the clinical investigation, to obtain consent from subjects prior to their enrollment in the clinical investigation, to collect and record data as required by the clinical investigation plan and case report forms, and to maintain document related to the clinical investigation for the period of time required.

Confidential

This document contains confidential information belonging to Medical Metrics Diagnostics, Inc. Except as may be otherwise agreed to in writing, by accepting or reviewing these materials, I agree to hold such information in confidence and not to disclose it to others (except where required by applicable law), nor use it for unauthorized purposes.

Investigator name (print)

Signature Date

SYNOPSIS

Investigation Title	The Sagittal Plane Shear Index (SPSI™) for deciding whether to fuse after decompressing a stenotic lumbar level
Sponsor	Medical Metrics Diagnostics, Inc.
Protocol Reference	SPSI-01
Investigational Device	Sagittal Plane Shear Index (SPSI™)
Overall Design	This is a prospective, multi-center, single arm clinical investigation
Device description	SPSI™ quantifies the sagittal plane translation per degree of rotation from high-quality flexion-extension radiographs of the lumbar spine.
Intended Use	SPSI™ will be used preoperatively in lumbar stenosis patients to objectively assess the sagittal plane translation per degree of rotation of the stenotic level.
Objective of the clinical investigation	To assess the proportion of lumbar spinal stenosis surgical treatment plans that change when an objective measurement of spinal stability is included and applied following a simple treatment algorithm
Investigation duration and number of visits	Total duration of the clinical investigation is 41 months: • Enrollment period: 14 months • Follow-up phase: 24 months • Total number of visits per subject: 4
Investigational Centers	3 centers in the Netherlands
Investigation Population	A total of 65 subjects will be included who have received surgery and where the post- SPSI™ surgical plan is in accordance with the SPSI™ metric. To ensure this, a maximum of 80 subjects may be recruited. Recruitment will be stopped when the required 65 subjects who have received surgery and where the post- SPSI™ surgical plan is in accordance with the SPSI™ metrics are included
Inclusion Criteria	1. Symptoms consistent with single level lumbar spinal stenosis based on judgment and experience of the investigator 2. Central and or foraminal stenosis confirmed by MRI as per the investigators clinical standards 3. Grades 1 (10 to 25%) or 2 (26 to 50%) anterior or retro-spondylolisthesis using the Meyerding scale 4. Absence of lateral spondylolisthesis 5. No prior lumbar spinal surgery 6. Absence of American Society of Anesthesiologists (ASA) class IV or higher disease 7. The single level surgical technique planned (prior to viewing the spinal motion report) to decompress the level is not expected to destabilize the spine (fusion is not deemed necessary due to probable iatrogenic instability) 8. Prior to viewing the spinal motion report, the surgical plan includes decompression or decompression and fusion of only one level 9. Based on the investigators subjective assessment, the patient is able to flex and extend sufficiently to facilitate acceptable flexion and extension radiographs

	10. The fusion technique planned prior to viewing the spinal motion report is the following: Instrumented posterior (pedicle screws and rods) with / without PLIF cage. 11. Subject is able to understand and sign the study Informed Consent Form 12. Subjects is at least 18 years of age. 13. Subject has willingness and ability to comply with study procedures and visit schedules and able to follow oral and written instructions
Exclusion Criteria	1) Lumbar stenosis without spondylolisthesis 2) Severe lumbar stenosis that requires a wide decompression where the investigator believes (based on experience and available research studies) that the decompression will destabilize the spine and fusion surgery is required regardless of preoperative SPSITM 3) Pregnant women 4) Scoliosis involving a lumbar curve greater than 10 degrees 5) Stenosis at the level of a transitional vertebra 6) Lateral spondylolisthesis (Coronal plane translational misalignment between vertebrae) 7) Prior lumbar spinal surgery 8) American Society of Anesthesiologists (ASA) class IV or higher disease
Primary Endpoint	The primary endpoint is the proportion of lumbar spinal stenosis treatment plans that change when SPSI™ results are used in establishing the surgical plan.
Secondary Endpoints	The secondary endpoint is the comparison of clinical outcomes (as measured by ODI and NRS leg pain) at 12 months and 24 months in lumbar stenosis patients where the surgical plan was in accordance with the SPSI™ metric compared to historical controls.
Exploratory Endpoints	• Does the presence of a facet fluid sign as indicated by the investigator on preoperative MRI correlate to instabilities specified by SPSI™ results? • What is the rate of instability (defined as a > 1 standard deviation increase in SPSITM) 12 months after decompression (no fusion) surgery, how do these rates compare to the published data and does the development of post-decompression instability have an effect on the change in ODI or NRS scores relative to preop? • What are the reoperation rates at 12 months following decompression alone and following decompression plus fusion, and how do these rates compare to published data from studies where similar inclusion and exclusion criteria were used and patients were randomized to decompression alone or decompression plus fusion? • Does a nonunion following decompression plus fusion surgery have an effect on the change in ODI or NRS scores relative to preop?

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ABBREVIATIONS

ADE	Adverse Device Effect
AE	Adverse Event
ASADE	Anticipated Adverse Device Effect
CI	Confidence Interval
CRF	Case Report Form
CRO	Contract Research Organization
CT	Computed Tomography
DMC	Data Monitoring Committee
EC	Ethics Committee
eCRF	Electronic Case Report Form
FDA	Food and Drug Administration
GCP	Good Clinical Practice
IB	Investigator Brochure
ICF	Informed Consent Form
IFU	Instructions For Use
IRB	Institutional Review Board
ISO14155	International Standard on the Clinical investigation of medical devices for human subjects — Good clinical practice
MedDRA	Medical Dictionary for Regulatory Activities
MDR	Medical Device Regulation
MRI	Magnetic Resonance Imaging
N	Number (typically refers to quantity of subjects)
NRS	Numeric Rating Scale
ODI	Oswestry Disability Index
PI	Principal Investigator
PT	Preferred Term
QA	Quality Assurance
QC	Quality Control
QSI	Quantitative Stability Index
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SOC	System Organ Class
SOP	Standard Operating Procedure
SPSI	Sagittal Plane Shear Index
TDPR	Translation per Degree of Rotation
UADE	Unanticipated Adverse Device Effect
USADE	Unanticipated Serious Adverse Device Effect

REVISION HISTORY

Version	Date	Summary of Changes/ Affected Sections
01	24-August-2018	Not applicable, first version
02	18-October-2018	Sample size has been updated, maximum allowed number of enrolled subjects added (section 5.3.8, section 6.5). Subject replacement (section 5.1.7) was updated to be in line with update in sample size. Sections 5.3.3 and 5.4.3.3 were updated to clarify subject withdrawal and study end.

1. INTRODUCTION

1.1. Lumbar Spinal Stenosis and Surgical Treatment Planning

Lumbar spinal stenosis is a relatively common medical problem, the clinical outcomes are often suboptimal (e.g. only about 50% reporting satisfaction with surgery at 2 years [1]), and the patient-specific, optimal treatment for the condition is poorly understood, due in part to a lack of diagnostic tests that have been validated to aid in treatment optimization [2]. Decompression surgery with or without additional fusion surgery are common surgical treatments. As reviewed by Machado et al, many prior research studies have concluded that there is at best marginal benefit to fusing a stenotic lumbar level following decompression, versus just decompressing the level [3]. These studies are summarized in recent, high-profile publications [1, 4]. The decompression part of the surgery is generally accepted as essential to achieving clinical benefit by relieving the physical source of stenosis. Fusion surgery, if indicated, is typically performed as part of an expanded surgical procedure (decompression plus fusion). However, avoiding fusion when it is not beneficial is important since fusion can add substantial expense and morbidity to the surgery [5, 6].

There are two generally accepted hypotheses for justifying fusion surgery in addition to decompression surgery. First, fusion is justified if the level being decompressed was unstable preoperatively. Unstable is typically defined as intervertebral motion above the range of motion expected in healthy and asymptomatic spines. Second, fusion surgery is justified if needed to prevent complications from iatrogenic instability that might be created by the decompression surgery.

The first justification is supported by studies documenting an association between abnormal intervertebral motion and symptoms. Correcting a known potential source of symptoms (abnormal intervertebral motion) during the same surgery used to correct the primary source of symptoms (stenosis) is rational. The challenge with the first justification has been the lack of a validated, objective test to diagnose and objectively quantify preoperative instability.

With respect to the second justification, there are some scientific publications that provide guidance to the surgeon to determine whether the decompression procedure may destabilize the spine [7, 8], although there is a lack of rigorous clinical validation studies. There is a range of techniques for decompressing the spine; some with a low probability of destabilizing the spine and others with a higher probability. The extent to which a decompression procedure may alter the stability of a spine can currently not be predicted with certainty.

Neither of these two justifications for supplemental fusion surgery has been validated by clinical studies, partly due to the lack of a validated diagnostic test for spinal instability. Surgeons are currently faced with the dilemma of whether or not to add fusion to a decompression procedure. Surgeons currently rely mostly on their experience to conclude if a level is unstable preoperatively or if a specific decompression procedure is likely to destabilize the spine.

As such, the preoperative determination of the stability of the spine is critical for the surgical planning for treatment of lumbar spinal stenosis. Unfortunately, although hundreds of peer-reviewed scientific publications address the challenge of reliably diagnosing spinal stability, no well-validated diagnostic test to reliably diagnosing spinal stability is currently in wide-spread clinical use. The facet fluid sign (high signal intensity in axial or sagittal sections through the facet joints) that can be seen in some MRI exams of the

lumbar spine is currently one of the best supported indicators for instability [9-11]. It should also be noted that gas can sometimes be seen in CT exams of the facet joints [12-14]. Gas in the facet joints is also an accepted indicator of instability [15], but gas would appear black on an MRI and would therefore be a false-negative. The MRI fluid sign may therefore have an unacceptable false-negative rate, although this has never been formally tested, also for lack of a gold-standard test for spinal instability. A validated test for spinal instability would facilitate research to determine whether instability measurements can be used choose the optimal surgical treatment for each level.

An objective metric called the Sagittal Plane Shear Index (SPSI™) has been recently described in the scientific literature [16]. This metric was labeled as the Quantitative Stability Index (QSI™) [16]. To avoid confusion between multiple intervertebral motion metrics, the metric that was previously labeled QSI™ is now being labeled as the Sagittal Plane Shear Index (SPSI™). The SPSI™ metric quantifies the sagittal plane intervertebral translation-per-degree-of-rotation (TPDR), and is reported as the number of standard deviations from the average found at radiographically normal levels in asymptomatic volunteers. The asymptomatic population that is used to define normal TPDR has been previously described [17]. Data for an additional 193 asymptomatic volunteers was added to this population to strengthen the definition of normal motion [18].

TPDR has previously been described as a potential metric for spinal instability [19], but was not extensively pursued following the 1990 publication for lack of a clinically practical and validated method measuring intervertebral translations and rotations in clinical practice. The SPSI™ metric can now be obtained in routine clinical practice using translation and rotation measurements obtained with validated computer-assisted methods (QMA®) [20-24]. SPSI™ is intended to be simple to use. According to the SPSI™ treatment planning algorithm, SPSI™ > 2 informs a clinician that the TPDR is > 2 standard deviations above the average TPDR in the asymptomatic population. This provides for an objective diagnostic indicator for spinal instability defined as a specific, well-defined intervertebral motion metric that is outside the 95% confidence interval established for asymptomatic volunteers. If SPSI™ is > 2 at a level where surgical treatment for stenosis is planned, then the clinician has objective evidence of abnormal motion and this may help to determine whether fusion should be completed in addition to the decompression surgery.

In conclusion: Spine fusion is used in addition to decompression surgery for lumbar spinal stenosis in order to prevent abnormal intervertebral motion causing associated symptoms. At the same time, if the intervertebral motion at the stenotic level is within normal limits prior to surgery, and it is unlikely that the decompression will compromise stability, only spinal decompression will be performed [25]. Fusion is not indicated if the spinal level is stable preoperatively.

The research proposed in this document is intended to address the need identified in a recent publication by Austevoll et al. [26], reporting on the effectiveness of decompression alone compared with additional fusion for lumbar spinal stenosis with degenerative spondylolisthesis. They concluded: *"…a considerable number of patients can be treated with decompression alone. A challenge in future studies will be to find the best treatment option for each patient."* SPSI™ is intended to be part of a solution to the challenge that Austevoll et al. describe.

1.2. Sagittal Plane Shear Index (SPSI™)

The device under investigation is the Sagittal Plane Shear Index™ (SPSI™). SPSI™ is intended to be used preoperatively to objectively assess the sagittal plane translation per degree of rotation of the stenotic level in lumbar spinal stenosis patients. SPSI™ is considered software as a medical device. The software is installed at MMI and will be used solely by trained analysts and technical staff at MMI. Investigational sites are required to electronically upload X-ray images of the spine to MMI, where these images are analyzed and SPSI™ is calculated using QMA®. The output of the system is a SPSI™ report containing a labeled X-ray image of the lumbar spine and corresponding SPSI™ data. This report is provided electronically to the investigational sites for use in the treatment planning of patients with lumbar stenosis.

The SPSI™ quantifies the magnitude of sagittal plane translation of the posterior-inferior corner of a vertebra in a direction defined by the superior endplate of the immediately inferior vertebra (Figure 1). The raw magnitude is first measured in units of percent endplate width (to control for variability on the size of the vertebra). This is then divided by the magnitude of intervertebral rotation (to control for variability in patient effort when asked to flex and extend). This ratio is then expressed as the number of standard deviations from the average TDPR that was found in asymptomatic volunteers with radiographically normal spines. SPSI™ > 2 informs a clinician that the TPDR is > 2 standard deviations above the average TPDR in the asymptomatic population. This provides for an objective diagnostic indicator for spinal instability defined as a specific, well-defined intervertebral motion metric that is outside the 95% confidence interval established for asymptomatic volunteers. The raw measurements of translation and rotation are obtained from lateral radiographs of the spine with the patient flexed forward and with the patient extended backwards. These measurements are obtained using a computerized system (QMA®, Medical Metrics, Inc) previously validated to have the accuracy and reproducibility required for measuring the small translations that occur in a healthy spine[20]. The measurement methods are also the same that were used to establish the level-specific TDPR expected in a healthy and asymptomatic spine.

The computerized system along with the generated SPSI™ report is considered software as a medical device (SaMD). According to the European Union Medical Device Regulation (MDR), this type of device should be treated as an *active device*. Since this software is intended to provide information which is used to take decisions with diagnosis, it is considered a class IIa device (Rule 11 in Annex VIII of the European Union MDR).

During the SPSI-01 clinical trial, the active production version of QMA used at Medical Metrics, Inc. to conduct regulated clinical trials business will be used to generate SPSI. At the start of the SPSI-01 clinical trial this will be version 1.35 or higher. The QMA version number used to generate SPSI will be specified on the SPSI report. New QMA versions will not change the validated algorithms used to generate SPSI.

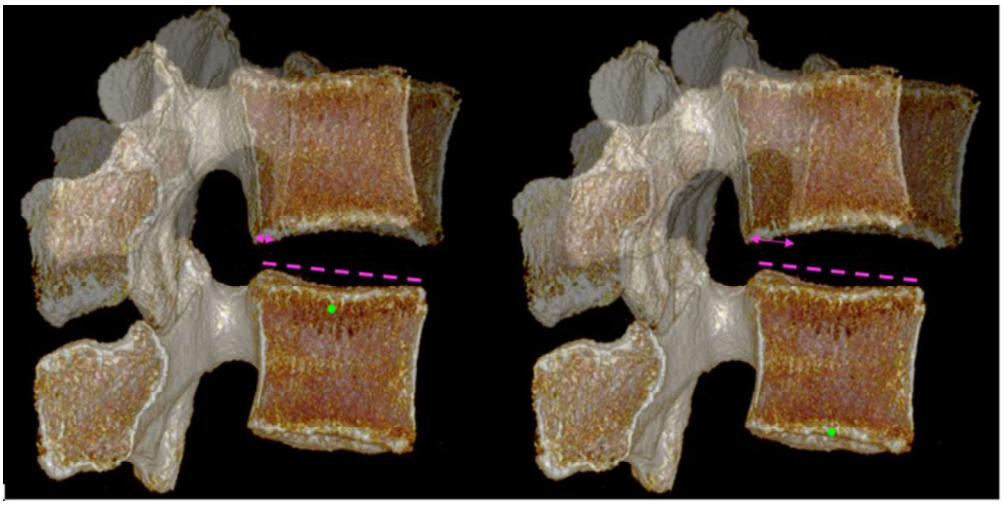

FIGURE 1: The sagittal plane intervertebral translation between the flexed and extended positions of the spine is illustrated below by the magenta arrows. The dashed lines represent the direction in which the translation is measured, and this is defined by the superior endplate of the inferior vertebra. On the left side is shown the translation expected in a healthy spine. On the right is shown the translation that can occur when spinal motion is abnormal. In both the left and right sides, there is 13 degrees of intervertebral rotation between the flexed and extended positions of the spine.

1.3. Manufacturer

The device is manufactured by Medical Metrics, Inc. (MMI). MMI is a medical imaging company located at 2121 Sage Rd, Suite 350, Houston, Texas, USA.

MMDx has contracted Medical Metrics, Inc. (MMI) to provide for importing of flexion-extension radiographs from the sites, for analyzing intervertebral motion using Quantitative Motion Analysis (QMA®) technology, and for calculating SPSI™. MMI has an established quality program for providing these services and for the software used to produce patient-specific reports that provide SPSI™ data. The MMI quality system will be relied on for the purposes of the clinical investigation. MMI will deliver the SPSI™ report to the clinical sites.

1.4. Intended Purpose of the Device in the Clinical Investigation

SPSI™ is intended to be used preoperatively to objectively assess the sagittal plane translation per degree of rotation of the stenotic level.

1.5. Intended populations and indication

With respect to the clinical investigation as detailed in this clinical investigation plan, the intended population are patients who have previously consented to surgical treatment for lumbar spinal stenosis, and the specific indication will be for objectively assessing the preoperative intervertebral motion.

1.6. Required Training and Experience

Investigators will be extensively trained in the use of the SPSI™ metric. During this training, investigators will be educated on all available current knowledge about SPSI™ and will engage in discussion with MMDx

scientists to address and resolve all issues. Investigators and MMDx scientists will review and discuss multiple lumbar stenosis case examples with imaging and SPSI™ reports and will identify any areas of question or concerns. This training will use methods similar to those used by Debono et al. [27]. The training will consist of the investigator developing an initial surgical plan after reviewing the imaging and clinical history. The investigator will then be provided with the SPSI™ report and will be asked to develop a second surgical plan. The investigators will then discuss these results with MMDx with specific emphasis on the changes to the surgical plan that the SPSI™ metric would support. The technicians at each site will be trained on how to obtain high-quality flexion and extension radiographs, that is where the subject has exerted sufficient effort when asked to flex and extend.

1.7. Technical Procedure: SPSI™

The SPSI™ metric requires good-quality lumbar flexion-extension radiographs. An imaging protocol and training materials to obtain high-quality flexion-extension radiographs will be provided to all investigational sites. Radiographs will be electronically sent to MMI, where they will be imported into previously validated computer-assisted Quantitative Motion Analysis (QMA®) measurement software [20-22, 24]. Using the QMA® software, intervertebral translation and rotation will be measured at the treatment level identified by the investigator as well as the other levels between the first lumbar and the first sacral vertebrae.

The subject will be withdrawn from the study if there is insufficient intervertebral rotation (< 5 degrees) at the treatment level to allow for a reliable assessment of SPSI™. This ≥ 5 degree threshold is required since without sufficient intervertebral motion, it is not possible to determine whether the intervertebral motion restraints are competent or whether abnormal motion can occur during flexion to extension. Motion < 5 degrees is considered to be within the neutral zone of intervertebral motion [28-30], where the spine is not sufficiently stressed to allow for detection of incompetent intervertebral motion restraints. SPSI™ will be reported as “NA” at any level where there is < 5 degrees of rotation. Additionally, if there is excessive out-of-plane imaging (the x-ray beam was so oblique to the sagittal plane of the spine such that the four corners of the vertebral bodies could not be reliably identified), or if the entire spine was not captured in either the flexion or extension radiograph, or if there was any other image quality problem that prevents a reliable calculation of SPSI™, at the level the investigator had intended to treat, then the subject will also be withdrawn from the study. In these cases, the SPSI™ for that level will be recorded as “NA” (not analyzable). These subjects will be withdrawn from the study and the end of the pre-surgery phase and will not receive any follow-up.

The QMA® software will calculate SPSI™ for each intervertebral level, as previously described, using normative reference data [17, 31]. A report that includes the SPSI™ metric will be completed and returned to the investigator within 3 business days of receipt of both the flexion-extension radiographs and the pre-SPSI™ surgical plan. MMI and MMDx will not have access to the pre- SPSI™ surgical plan until after the SPSI™ report has been delivered to the investigator.

Prior to providing the investigator with the SPSI™ report, the investigator must record and submit a initial surgical plan (pre-SPSI™ surgical plan)detailing whether they plan to perform only decompression surgery, or decompression plus fusion, along with the specific level that they plan to treat.

The SPSI™ report will be provided to the investigator no sooner than 24 hours after they submit the pre-SPSI™ surgical plan. This is to reduce potential bias from resistance to changing a plan that was just completed. After the investigator receives and reviews the SPSI™ report, the investigator will record a second surgical plan (the post-SPSI™ surgical plan).

TABLE 1. APPLICATION OF PREOPERATIVE SPSI™ IN ESTABLISHING A TREATMENT PLAN FOR LUMBAR SPINAL STENOSIS.

Level	Pre-SPSI™ Surgical Plan	Preop SPSI™ metric	Post-SPSI™ Surgical Plan	Surgical Plan Changed?
Stenotic	Decompress	<2	Decompress	No
Stenotic	Decompress	>2	Decompress & Fuse	Yes
Stenotic	Decompress & Fuse	<2	Decompress	Yes
Stenotic	Decompress & Fuse	>2	Decompress & Fuse	No

2. JUSTIFICATION FOR CLINICAL INVESTIGATION DESIGN

The design of the clinical investigation addresses the well-documented clinical need for a practical diagnostic test to allow a investigator to determine the stability of a level in the lumbar stenotic spine. The extensive number of clinical studies that have been conducted to assess whether decompression alone or decompression plus fusion is the best treatment option for patients diagnosed with lumbar stenosis is evidence for the desire for help in selecting the best treatment option. The primary reason for spine fusion surgery is to stop motion between vertebrae, and the primary justification for stopping motion is abnormal intervertebral motion. Several expert reviews conclude there is currently no validated metric for abnormal intervertebral motion. After those reviews were published, the Sagittal Plane Shear Index (referred to as QSI in the publication) was validated against the facet fluid sign [31]. The facet fluid sign is an indirect and imperfect diagnostic for abnormal motion, so the validation study is limited to showing the association between a high SPSI^{TM} and the presence of the facet fluid sign. A clinical investigation is needed to test the potential clinical efficacy of SPSI^{TM} in diagnosing abnormal motion, in order to use this diagnosis in the decision process on whether to add fusion to decompression of a stenotic lumbar level.

2.1. Pre-Clinical Software Validation and Testing

The QMA software platform and SPSI^{TM} has been developed, validated, and maintained in accordance with standard operating procedures that adhere to IEC 62304 (IEC 62304:2006 Medical device software – software life cycle processes) standards. This process includes:

• Verification and Validation

The process of development, verification and validation of the QMA V1.34 software is described in the software development plan “Verification & Validation of QMA V1.34” (Document No.: 02-134-01, Rev. No. 1, 21 May 2018). This process is in accordance with MMI SOP SOP-100 “Software Development”. The scope of this development plan is limited to changes from QMA version 1.33 to 1.34.

• Software Requirements and Change Control Matrix

The software requirements and change control matrix for the QMA V1.34 software development is described in “Software Requirements & Change Control Matrix of QMA V1.34” (Document No.: 02-134-02, Rev. No.: 1, 21 May 2018).

This document contains all software requirements for the QMA V1.34 software development project and documents the relationships between OnTime defects and features approved in the 31-Jul-2017 Change Control meeting (OnTime is the mechanism that MMI uses to document software modifications requested by end users to the QMA system architect based on regular production use).

• System Test Plan & Report

The System Test Plan & Report for QMA V1.34 (document no.: 02-134-04B, rev. no.: 1, 21 May 2018) contains the steps required to perform User Acceptance Testing and Software System Test for the QMA V1.34 software development project. This document also describes the steps required to build the QMA

V1.34 software from the source code to the installation-ready components using Microsoft Visual Studio 2010, version 10.0.30319.1.

The document reports that the software passes all tests and no fails were reported during user acceptance testing and software system testing. The document concludes that the QMA V1.34 software is authorized to be released for installation.

• **Installation Plan & Report**

Methods for installation, testing and documenting of the installation of QMA v1.34 is described in the "Installation Plan & Report for QMA V1.34" (Document No.:02-134-06, Rev. No.:1, 24 May 2018).

The document reports that the installation of the QMA v1.34 software passes all required installation steps as described in this document and no warnings and errors or deviations were found.

Furthermore, the document concludes that the Verification & Validation protocol for QMA V1.34 has been successfully executed and that the software QMA V1.34 is approved for use.

2.2. Prior Clinical Results

Weiler et al. reported that the sagittal plane intervertebral translation divided by the intervertebral rotation, measured from flexion-extension radiographs, is significantly higher in symptomatic low-back patients compared with controls [19].

The reproducibility of the QMA® measurements of intervertebral motion, that are required to calculate SPSI™, has been documented in clinical research [21]. The QMA® technology has also been used in many spine research studies as evidenced by the over 120 peer-reviewed publications and several hundred abstracts that have included measurements made using QMA® (see "Scientific Papers and Publications Featuring Medical Metrics Technology and Methods")This provides evidence that this technology is well-accepted.

The normative data required to calculate SPSI™ were established by collecting, sagittal plane translation-per-degree-of-rotation measurements for several hundred asymptomatic volunteers that did not have current back pain, never had any sustained back pain, and never sought treatment for back pain. One set of these data have already been published [17], and the other set reported in a recent abstract [18]. These data provide the normative reference data essential to calculating SPSI™. SPSI™ provides clinicians with the number of standard deviations away from the average translation-per-degree-of-rotation found in healthy spines. In the two studies, the flexion-extension studies were collected using standardized protocols. In the later study, the "walker" method was used to obtain the flexion-extension radiographs, and all 193 volunteers watched an educational video describing the protocol (https://youtu.be/20x0Mak1tc8) before they went for the collection of flexion and extension radiographs. The protocol was successful, with 95% of the flexion-extension studies have at least 5 degrees of intervertebral rotation at every level. That study validates the flexion-extension protocol that will be used with subjects in the proposed study.

A validation study using clinical data has been published showing the association between SPSI™ and the facet fluid sign [31]. This is important in that the facet fluid sign is currently the best-available diagnostic marker for potential instability [32]. Bogduk observed that instability occurs when there is too much

translation relative to the amount of rotation [33]. Hipp et al described additional reasoning and rationale for using the translation-per-degree-of-rotation as a metric for lumbar spinal instability [31].

MMI serves as the imaging core laboratory for many clinical trials and managed and analyzed all of the imaging from multiple large lumbar stenosis studies. MMI performed exploratory analysis on behalf of the sponsors of the clinical trials to identify potentially valuable insights into their data. This analysis revealed that, preoperatively, 25% to 30% of lumbar stenosis patients had SPSI^{TM} >2, at the levels that were identified for surgical treatment by a surgeon. This proportion was consistent across multiple studies. Approximately 40% of these patients had SPSI^{TM} >2 at some level in the spine (treated or adjacent levels). This proportion is also consistent across studies. This supports that there was un-diagnosed instability at some of the untreated adjacent levels. Untreated instability could compromise clinical outcomes, although this hypothesis remains untested for lack of a validated diagnostic test for instability. Note that not all adjacent levels were analyzed in all of the studies, so the proportion of un-diagnosed adjacent level instability may have been higher than 40%.

In one of the large lumbar stenosis clinical trials where clinical outcome data were made available to MMI, preoperative SPSI^{TM} was calculated at the treatment level in the control group. The control group subjects had all been treated using decompression and posterior-lateral fusion. The clinical outcomes data were made available to scientists at MMI after all of the data required by the United States Food and Drug Administration (FDA) had been provided to the FDA. The data were then analyzed to determine whether preoperative intervertebral motion was predictive of treatment outcomes at the two-year follow-up. Only single level fusion cases were analyzed to avoid the challenge of differentiating which level was influencing outcome scores. That analysis documented enhanced treatment benefit when the preoperative SPSI^{TM} was > 2, using threshold-limit graphical data analysis[34]. In the FDA study, subjects were considered to have received a benefit from fusion surgery if the patient had at least a 15 point improvement in the Oswestry Disability Index (ODI). With all data pooled together (regardless of preoperative SPSI^{TM}), the proportion of patients that achieved the ≥ 15 point improvement in ODI was determined. That defines the pooled subject treatment benefit. An enhanced treatment benefit was defined as when the proportion of patients achieving the ≥ 15 point improvement in ODI was at least 15 percent greater than the pooled subject treatment benefit. A ≥ 15 percent improvement over the pooled subject treatment benefit was statistically significant. This analysis supports that if fusion was restricted to only those patients with SPSI^{TM} > 2, the ODI scores would be significantly higher than when fusion was used in all patients regardless of the preoperative SPSI^{TM}. This was a preliminary observation based on retrospective analysis of prospectively collected data, but supports the potential clinical utility of SPSI^{TM} for selecting which levels to fuse. These results may justify a clinical trial to more formally test the hypothesis that preoperative SPSI^{TM} can be used to help select the optimal surgical treatment for each patient. However, it must first be documented that preoperative SPSI^{TM} will change the surgical treatment plan in a significant number of patients.

3. RISKS AND BENEFITS OF THE INVESTIGATIONAL DEVICE AND CLINICAL INVESTIGATION

3.1. Anticipated Clinical Benefits

Anticipated clinical benefits of the use of the device would be improved reduction in preoperative symptoms and lower probability of reoperation. The potential for improved reduction in preoperative symptoms may occur if the investigator was planning to perform decompression plus fusion surgery prior to learning that SPSI™ was < 2 for the stenotic level, and then performed only decompressive surgery. That could avoid symptoms associated with unnecessary fusion surgery. The potential for improved reduction in preoperative symptoms might also occur if the investigator was planning only decompression surgery prior to learning that SPSI™ was > 2 for the stenotic level, and then performed fusion in addition to decompression surgery. In that scenario, the post-operative symptoms that a patient could experience related to the instability could be prevented by alerting the investigator to instability that they did not appreciate without SPSI™.

3.2. Residual Risk associated with the use of SPSI™

A risk analysis was performed according to the International Medical Device Regulators Forum (IMDRF) guidelines for risk categorization of Software as a Medical Device (SaMD) (SaMD N12 *Software as a Medical Device: Possible Framework for Risk Categorization and Corresponding Considerations*, 18 September 2014). The risk analysis identified nine hazards. After risk mitigation, four hazards were considered Acceptable and five were considered As Low As Reasonably Possible. Additionally, the overall system/entity was also considered broadly for risk and was determined to be acceptable.

3.3. Anticipated Adverse Device Effects

Diagnostic use of SPSI™ does not establish a diagnosis or treatment plan, but rather is used by the physician as one of several indicators to drive diagnosis and/or treatment planning. As a result, the use of SPSI™ can lead to improper treatment decision leading to an incorrect type of surgical intervention, or lack of surgical intervention. This may lead to the following Anticipated Adverse Device Effects:

Subject received fusion when the surgeon would have only performed a decompression if they did not use the SPSI™ report:

- Failure of the fusion device/procedure to improve symptoms and/or function more than would have been achieved by decompression alone
- Pain and discomfort associated with the operative site or presence of fusion device
- Sensitivity or allergy to the materials used in the fusion device
- Infection related to implantation of the fusion device
- Re-operation to remove or replace the fusion device
- Wear debris from the connections between components of the fusion hardware which may damage surrounding soft tissues including muscle or nerve
- Scar tissue may form at the fusion site and may contribute to symptoms
- Malposition of the fusion device that may contribute to symptoms
- Malalignment of anatomic structures that may contribute to symptoms

- Migration or dislodgement of fusion device from the original position so that it becomes ineffective or causes damage to adjacent bony soft tissues including nerve
- Fusion device may loosen, fatigue, deform, break, or disassemble which may require another operation to remove the fusion implant, and may require another method of treatment
- Pseudoarthrosis (non-union)
- Adjacent level instability and/or degeneration

Subject did not receive fusion when the surgeon would have done fusion surgery if they did not use the SPSI™ report:

- Failure of decompression surgery alone to improve symptoms and/or function as much as would have occurred if both decompression and fusion had been performed
- Additional surgery, such as fusion, performed at the treated level
- Increased spinal instability after surgery that may contribute to symptoms
- Loss of spinal alignment that may contribute to symptoms
- Disc herniation that may contribute to symptoms
- Osteophyte formation that may contribute to symptoms
- Facet joint degeneration that may contribute to symptoms

3.4. Risks associated with lumbar flexion-extension radiographs

The high-quality flexion-extension radiographs required for this study may add risk to the patient, as obtaining these radiographs require exposure to x-rays that the patient might otherwise not be exposed to. The effective dose for a typical flexion-extension x-ray study of the lumbar spine is 1.5 mSv [35]. Each subject participating in the clinical investigation would have two lumbar flexion-extension x-ray exams. Each exam would consist of one flexion and one extension radiograph. Based on a large clinical investigation on the risk to develop cancer associated with exposure to radiation, it was estimated that the excess relative risk for cancer development is 0.97 per Sv [36]. The excess relative risk of the radiation that each subject would receive from participation in this clinical investigation is therefore calculated as 0.97/Sv * 3 mSv * 1 Sv/1000 mSv = 0.00291. To place the radiation risk estimate for this clinical investigation into perspective, a person will be exposed to 0.035 mSv of radiation during a typical United States coast-to-coast round-trip airplane flight[1]. There are many sources of exposure to radiation in daily living and the public is exposed to approximately 3 mSv/year from ubiquitous radiation [37].

3.5. Risk Mitigation

Investigators in the clinical investigation can choose not to implement a change in the surgical plan that the per-protocol use of preoperative SPSI™ would require (as described in Table 1). For example, if the SPSI™ metrics for the stenotic level suggest that there is abnormal intervertebral motion and that fusion should be added to the decompression surgery, but the investigator is certain that the level is stable or that there is another reason not to add fusion surgery, then the investigator is free to do what they believe is best for the subject. In that scenario, the investigator would record the specific reason for not following

[1] https://www.cdc.gov/nceh/radiation/air_travel.html

the clinical investigation plan. The experience and clinical judgement of the investigator will help to mitigate risk.

Furthermore, potential risks associated with participation in this clinical investigation will be minimized and managed in accordance with ISO 14155 Clinical Investigation of Medical Devices for Human Subjects – Good Clinical Practices, and requirements of the approving Ethics Committee(s).

3.6. Risk-to-Benefit Rationale

MMDx believes that, due to the wide variability in treatment selection and clinical outcomes for surgical treatment of lumbar stenosis [27, 38], resulting in part from lack of validated guidelines for selecting the optimal surgical treatment [39], the risks to a subject if they participate in this clinical investigation are within the inherent risks of lumbar stenosis surgery in general. For example, the SPSI™ metrics may indicate that a stenotic level is stable and the investigator may then only decompress the level where they originally planned to both decompress and fuse that level. Alternatively, after reviewing the SPSI™ metrics, the investigator may fuse a level they would otherwise only be decompressed. Due to these potential changes, there is a potential need for a subsequent surgery or non-surgical treatment that might otherwise have been avoided. Given the lack of clear guidelines on how to select the optimal surgery for lumbar stenosis [39], and the wide variability in surgical techniques in use, the residual risks from participating in the clinical investigation are considered similar to the risks associated with having selected a different investigator for treatment.

However, the available literature supports that if the patient had selected a different surgeon, that surgeon may have chosen to only decompress the level. The SPSI™ metric therefore resulted in a change in treatment plan that is within expected surgeon-to-surgeon variability. Lumbar stenosis patients have been randomized to either decompression only or decompression plus fusion in many prior clinical trials [3]. The many prior studies are evidence that the possible of risk of not choosing the optimal surgery for patient is acceptable in pursuit of the goal of discovering how to select the best surgery.

MMDx firmly believes that the benefits of the SPSI™ outweigh the potential risks posed to participating subjects.

4. OBJECTIVE AND HYPOTHESIS

The primary objective of this clinical investigation is to determine if the SPSI™ metric calculated from preoperative flexion-extension radiographs will change the surgical treatment plan that was initially recorded before accessing the SPSI™ data.

The associated hypothesis is that use of SPSI™ will provide an objective stability metric that will change the surgical plan in a significant proportion of subjects. These changes can include the decision to fuse a level that was previously planned to only be decompressed, or to decompress a level that was previously planned to be decompressed and fused.

As a secondary objective of the current clinical investigation, clinical outcome data will be collected to test the hypothesis that the use of the preoperative SPSI™ at the treatment level will result in improved clinical outcomes. The sample size for the current study is unlikely to be sufficient to test this hypothesis with a high level of statistical power, yet the data will help with design of subsequent research.

The outcomes from this clinical investigation will serve as input for a subsequent clinical investigation to investigate the hypothesis that planning surgical treatment using the preoperative SPSI™ at the treatment level(s) will result in improved clinical outcomes and a reduction in healthcare costs.

5. DESIGN OF THE CLINICAL INVESTIGATION

5.1. General

This is a prospective, multi-center, single arm clinical investigation to assess the proportion of lumbar spinal stenosis surgical treatment plans that change when an objective measurement of spinal stability is included and applied following a simple treatment algorithm.

5.1.1. Minimization of Bias

This will be a single-arm clinical investigation where each investigator records a surgical plan (preprior to having access to the SPSI™ results, and then approves or rejects changes to the treatment plan based on the results of the SPSI™ metrics. Medical Metrics will provide the SPSI™ report prior to having access to the investigator's initial treatment plan. If the investigator rejects any changes to the surgical plan that would be required by an algorithmic application of the SPSI™ results, the investigator will be required to record a justification for the rejection. Any bias against the SPSI™ results would be evidence in a systematic rejection of changes required by an algorithmic application of the SPSI™ results.

5.1.2. Primary Endpoints

The primary endpoint is the proportion of lumbar spinal stenosis treatment plans that change when SPSI™ results are used in establishing the surgical plan.

This endpoint was chosen for the current study, since the outcome is critical to the design of subsequent research to answer the more important question of whether use of preoperative SPSI™ to select the optimal surgical treatment can improve clinical outcomes for patients. If the SPSI™ metric rarely changes the surgical plan, it may not be worth further pursuit of the SPSI™ metric. Conversely, if the SPSI™ metric changes the plan in a significant proportion of cases, then that knowledge can be used to help design subsequent research.

5.1.3. Secondary Endpoints

The secondary endpoint is the comparison of clinical outcomes (as measured by Oswestry Disabilty Index (ODI) and Numeric Rating Scale (NRS) leg painleg pain) at 12 months and 24 months in lumbar stenosis patients where the surgical plan was in accordance with the SPSI™ metric compared to historical controls.

If the SPSI™ metrics change the surgical treatment plan in a significant proportion of cases, the next question is whether the changes that the SPSI™ metrics support can lead to improved clinical outcomes, reduced reoperation rates, reduced use of pain medications and other clinical benefits. Without first documenting that investigators will use the SPSI™ metrics to change the surgical treatment plan, a clinical study to determine if the SPSI™ metrics can improve outcomes was not justified. However, the results of the proposed study will provide data that can be analyzed for evidence to support the hypothesis that use of SPSI™ metrics can help to decide if fusion should be performed in addition to decompression of a stenotic lumbar level. That analysis will be valuable in the design of subsequent research.

5.1.4. Exploratory Endpoints

The following exploratory endpoints will be assessed:

- Does the presence of a facet fluid sign as indicated by the investigator on preoperative MRI correlate to instabilities specified by SPSI™ results?
- What is the rate of instability (defined as a > 1 standard deviation increase in SPSI™) 12 months after decompression (no fusion) surgery, how do these rates compare to the published data (for example Guha et al [40] and Cushnie et al [41]), and does the development of post-decompression instability have an effect on the change in ODI or NRS scores relative to preop?
- What are the reoperation rates at 12 months following decompression alone and following decompression plus fusion, and how do these rates compare to published data from studies where similar inclusion and exclusion criteria were used and patients were randomized to decompression alone or decompression plus fusion [3, 42]?
- Does a nonunion following decompression plus fusion surgery have an effect on the change in ODI or NRS scores relative to preop?

5.1.5. Safety Endpoint

The safety endpoint will be the nature and frequency of all adverse events observed during the clinical investigation including their timing, severity and relatedness to the investigational device and/or clinical investigation procedures.

5.1.6. Equipment for Assessment

High-quality flexion and extension radiographs are required for all subjects, both preoperatively and at 12 months follow-up. High-quality is defined as visualizing all levels from L1 to S1 and having at least 5 degrees of intervertebral rotation between flexion and extension, and the ability to clearly identify the four corners of each vertebra in both the flexion and extension radiographs. All radiographs must be provided in digital format, with images created by either a computer radiography or digital radiography system. Photographs of an x-ray on a view box are not acceptable. During site-screening, the x-ray equipment that will be used to collect the flexion-extension radiographs will be assessed for ability to provide the required quality. That includes the ability to easily position the x-ray source and detector to capture the spine in the fully flexed and fully extended positions, the ability to transmit x-rays to MMI in digital format, as well as the ready availability of a walker required for patient support during image acquisition.

5.1.7. Subject Replacement

An enrolled subject will be replaced if 1) the subject fails screening, 2) the subject does not receive surgery or 3) the level intended to be treated in the subject is indicated as not analyzable in the SPSI™ report.

5.2. Investigational Device and Comparators

No comparator device will be used to address the endpoint s of this study.

5.3. Subjects

5.3.1. Inclusion Criteria

1) Symptoms consistent with single level lumbar spinal stenosis based on judgment and experience of the investigator

2) Central and or foraminal stenosis confirmed by MRI as per the investigators clinical standards
3) Grades 1 (10 to 25%) or 2 (26 to 50%) anterior or retro-spondylolisthesis using the Meyerding scale [43]
4) Absence of lateral spondylolisthesis
5) No prior lumbar spinal surgery
6) Absence of American Society of Anesthesiologists (ASA) class IV or higher disease
7) The single level surgical technique planned (prior to viewing the spinal motion report) to decompress the level is not expected to destabilize the spine (fusion is not deemed necessary due to probable iatrogenic instability)
8) Prior to viewing the spinal motion report, the surgical plan includes decompression or decompression and fusion of only one level
9) Based on the investigators subjective assessment, the patient is able to flex and extend sufficiently to facilitate acceptable flexion and extension radiographs
10) The fusion technique planned prior to viewing the spinal motion report is the following: Instrumented posterior (pedicle screws and rods) with / without PLIF cage
11) Subject is able to understand and sign the study Informed Consent Form
12) Subjects is at least 18 years of age.
13) Subject has willingness and ability to comply with study procedures and visit schedules and able to follow oral and written instructions

5.3.2. Exclusion Criteria

9) Lumbar stenosis without spondylolisthesis
10) Severe lumbar stenosis that requires a wide decompression where the investigator believes (based on experience and available research studies) that the decompression will destabilize the spine and fusion surgery is required regardless of preoperative SPSI™
11) Pregnant women
12) Scoliosis involving a lumbar curve greater than 10 degrees
13) Stenosis at the level of a transitional vertebra
14) Lateral spondylolisthesis (Coronal plane translational misalignment between vertebrae)
15) Prior lumbar spinal surgery
16) American Society of Anesthesiologists (ASA) class IV or higher disease

5.3.3. Subject Withdrawal, Discontinuation and Study End

A subject may withdraw or discontinue its participation at any time during the clinical investigation. He/she does not have to give a reason for withdrawal. Subjects may also be withdrawn from the clinical investigation by the investigator for non-compliance with clinical investigation plan, due to adverse events or if the investigator feels it is in the subject's best interest to stop. Subjects withdrawn due to an adverse event will be followed until resolution of the adverse event or 30 days, whichever is the shorter time.

In addition, a subject will be withdrawn from the study when:

- Subject does not comply with inclusion and exclusion criteria.

- The stenotic level intended to be treated in the subject is indicated as not analyzable in the SPSI™ report.
- Subject will not receive surgery.
- Subject is lost to follow-up.

Subjects will be replaced in accordance with section 5.1.7. The reason for subjects' withdrawal or discontinuation will be recorded. Any data collected up until the time of withdrawal of the subject will be used for analysis.

Study participation of the subject will end when:

- The post-SPSI™ surgical plan is inconsistent with the SPSI™ report. In this case the subject will end participation in the study after the surgery has been performed.
- Subject has completed the 24 months follow up visit.

After study end, subjects will receive medical care according to standard of care, if applicable.

5.3.4. Enrollment

A subject is considered enrolled in the clinical investigation after they have provided written informed consent. A subject is considered treated per algorithm if the post- SPSI™ surgical plan is in accordance with the SPSI™ metric and if the subject has received surgery. A subject who is enrolled in the clinical investigation, but does not comply with the inclusion and exclusion criteria is considered a screen-failure.

5.3.5. Total expected duration of the clinical investigation

The clinical investigation is expected to take approximately up to 41 months including the enrollment period.

5.3.6. Expected duration of subject's participation

Time from the subject's consent for participation in the clinical investigation until surgery is up to 3 months. Subjects will be followed for two year after surgery. The total expected duration is therefore up to up to 27 months.

5.3.7. Enrollment period

The enrollment period is expected to take approximately 14 months.

5.3.8. Number of Subjects

A total of 65 subjects will be included who have received surgery and where the post- SPSI™ surgical plan is in accordance with the SPSI™ metric. To ensure this, a maximum of 80 subjects may be recruited. Recruitment will be stopped when the required 65 subjects who have received surgery and where the post- SPSI™ surgical plan is in accordance with the SPSI™ metrics are included.

5.4. Procedures

5.4.1. Schedule of Assessments

TABLE 2. SCHEDULE OF ASSESSMENTS

Assessment	Visit 1 Screening (≤ 3m to surgery)	Pre-surgery phase	Visit 2 Surgery	Visit 3* 6m (±30d)	Visit 4 12m (±30d)	Visit 5 24m (±30d)
Informed Consent	X					
Demographics	X					
Medical History	X					
MRI	X#					
Flexion/Extension X-rays	X				X	
Surgical Plan – pre SPSI™ (P1)		X				
SPSI™ metric		X			X	
Surgical Plan – post SPSI™ (P2)		X				
Actual Surgery Performed (P3)			X			
Oswestry Disability Index	X			X	X	X
Numeric Rating Scale leg pain	X			X	X	X
Patient satisfaction				X	X	X
Collection of reoperation data					X	X
Collection of analgesic use data	X				X	X
Collection of Adverse Event data			X		X	X

MRI done as part of standard of care.

*This visit can be done over the phone.

5.4.2. Visit 1 - Screening (≤3m to surgery)

Consecutive lumbar stenosis patients that are planned to undergo lumbar decompression surgery or lumbar decompression plus fusion (based on symptoms, MRI-based confirmation of stenosis and severity of stenosis, and the investigator's current clinical decision making process), will be asked to participate in the clinical investigation. Subjects must have an MRI exam available (performed per standard of care) that was used to confirm stenosis, as well as images that were used to document spondylolisthesis per the investigator's standard of care. Prior to performing any activities/evaluations related to the clinical investigation, except the standard of care assessments, the subject must be thoroughly informed about all aspects of the study, including scheduled visits and activities, and must have signed the informed consent approved by the Ethics Committee. The screening visit may occur at any time within 3 months prior to surgery.

During the screening visit the following assessments will be performed:

5.4.2.1. Informed Consent

Informed consent procedure will be performed as described in section 14.

5.4.2.2. Demographics

Recording of patient baseline characteristics (e.e. age, gender, race, ethnicity) will be completed at screening.

5.4.2.3. Medical History

Recording of the subject's relevant medical history (up to 5 years prior to screening) will be completed. Medical history is considered relevant when related to any of the study eligibility criteria, when it may influence the conduct of the study, or when it may affect any of the study endpoints, at the discretion of the investigator.

5.4.2.4. Standard of care MRI

A standard of care MRI exam will be used to confirm stenosis. The MRI exam is considered standard-of-care in the management of spinal stenosis patients as it is the primary tool for verifying the presence and extent of stenosis. This MRI will also be used to determine the presence of facet fluid sign. The facet fluid sign is observation of an abnormally wide area of high signal intensity in the left and/or right facet joints. The observations will be done by the investigator.

5.4.2.5. Pre-surgery Flexion-Extension Radiographs

Flexion-extension radiographs will be obtained following a study-specific radiographic protocol to help assure that all x-rays will be of high-quality. The subject will be asked to watch a training video available on YouTube prior to collection of the radiographs. The training video will help to assure that the subject is aware of what is required of them to obtain radiographs of high-quality. During image acquisition, the subject will be asked to stand in front of a standard walker. Using the walker for support, the subject will bend forward as instructed in the video, and the flexion radiograph will be obtained. The subject will then be asked to use the walker for support as they bend backwards, as instructed in the training video, and the extension radiograph will be obtained. The flexion and extension radiographs will be electronically sent to MMI for analysis. The site will be responsible for assigning a study-specific identification number to the subject, and for providing that study-specific number to MMI along with the flexion and extension radiographs.

5.4.2.6. Oswestry Disability Index

The Oswestry Disability Index (ODI) version 2.1a is a validated patient reported outcome and is used to indicate the extent to which a person's functional level is restricted by disability. The ODI consist of ten topics concerning intensity of pain, lifting, ability to care for oneself, ability to walk, ability to sit, sexual function, ability to stand, social life, sleep quality, and ability to travel. Each topic has 6 potential answers consisting of statements related to the topics. The subject checks the statements which most closely resembles their situation. Each question is scored on a scale of 0–5 with the first statement indicating the least amount of disability (scored 0) and the last statement indicating most severe disability (scored 5). The scores for all questions answered are summed, then multiplied by two to obtain the index (range 0 to 100). Zero equates to no disability and 100 relates to the most severe disability. The ODI will be collected on paper after which it will be entered into the electronic case report form (eCRF).

5.4.2.7. Numerical Rating Scale leg pain

The Numeric Rating Scale (NRS) leg pain is a patient reported outcome and is used to measures a person's pain intensity with respect to leg pain. Subjects are to indicate on a scale from 1 to 10, the average pain

experienced in the previous week. Zero is equated to no pain and 10 equates to worst pain possible. The NRS leg pain will be collected on paper after which it will be entered into the eCRF.

5.4.2.8. Analgesic Use

Current analgesic use will be recorded at screening, 12 months and 24 months. The analgesic use questions as described by Clement *et.al*.[44]will be used to collect this information. Subjects will be asked if they use narcotic or non-narcotic pain relieving medication for their back problems, "yes regularly", "yes sometimes", or "no".

5.4.3. Pre-surgery phase

5.4.3.1. Pre-SPSI™ Surgical Plan

After the screening visit, the investigator will complete an pre- SPSI™ surgical plan. This pre- SPSI™ surgical plan will document the type of operation (decompression or decompression plus fusion) that would be performed at the operative level based on the investigator's standard of care decision making. This pre- SPSI™ surgical plan will be entered by the investigator into the eCRF and collected by the CRO managing the study. This surgical plan must be provided to the CRO before the SPSI™ report is provided to the investigator.

5.4.3.2. SPSI™ Report

The preoperative flexion-extension radiographs will be sent to MMI and the intervertebral motion will be analyzed using QMA®. To avoid any possibility of bias, MMI will not be informed what level the investigator intends to treat. Every level in the lumbar spine, from L1-L2 to L5-S1 will be analyzed. If there is insufficient intervertebral motion to reliably calculate SPSI™ (< 5 degrees), or if there is excessive out-of-plane, or if not the entire spine was captured in either the flexion or extension radiograph, or if there was any other image quality problem that prevents a reliable calculation of SPSI™, then the SPSI™ for that level will be recorded as "NA" (not analyzable). When the site receives the SPSI™ report, the investigator will determine whether SPSI™ is reported at NA at the level the investigator had intended to treat. These subjects will be withdrawn from the clinical investigation at the end of the pre-surgery phase and will not receive any follow-up. In the event of subject being withdrawn from the study as a result of SPSI™ being reported as NA, the flexion/extension protocol will be re-reviewed with the site to determine if interventions can be implemented at the site to avoid further situations where SPSI™ cannot be reliably calculated.

A SPSI™ report that provides SPSI™ will be completed and returned to the investigator after 24h, but within 3 business days of receipt of the flexion-extension radiographs at MMI and recording of the initial pre-SPSI™ surgical plan at the CRO.

5.4.3.3. Post- SPSI™ Surgical Plan

Based on review of the SPSI™ report, the investigator will determine if the pre-SPSI™ surgical plan needs to be modified as described in Table 1 of this clinical investigation plan. The investigator will review any modifications to the pre-SPSI™ surgical plan and integrate the information in the SPSI™ report along with their knowledge of the spine motion metrics and all other information that they obtain from the available imaging (MRI, CT, radiographs as per their standard clinical practice) to make a decision about which levels

to treat and what operation to perform at the stenotic level. The investigator will then complete a post-SPSI™ surgical plan. By comparing the post-SPSI™ surgical plan with the pre-SPSI™ surgical plan, a determination will be made, per Table 1, whether the SPSI™ report resulted in a change in the surgical plan. Those data will be used to address the primary endpoint: What proportion of surgical treatment plans were changed after integrating SPSI™ metrics into the planning process.

In addition, if the post-SPSI™ surgical plan is inconsistent with the SPSI™ report (e.g. SPSI™ report indicates instability but the investigator plans to decompress only, or SPSI™ report indicates stability but the investigator plans to decompress and fuse), the investigator will be asked to record the reason (e.g. SPSI™ report indicates instability but there is a contraindication to fusion; or SPSI™ report indicates stability but there is excessive fluid in the facet joint, suggesting instability, so level will be fused). If the post-SPSI™ surgical plan is inconsistent with the SPSI™ report, the subject will end participation in the study after the surgery has been performed.

5.4.4. Visit 2 - Surgery

Surgery will be performed according to the post-SPSI™ surgical plan . Decompression and fusion surgery will be conducted according to standard hospital procedures. After the surgery is complete, the investigator records any deviations and reason for deviations from the post-SPSI™ surgical plan. For example, whereas the investigator may have planned to only decompress a level, they may find during surgery that a more extensive decompression was required than originally anticipated, and that requires fusion to avoid iatrogenic instability. Deviations from the post-SPSI™ surgical plan are not considered protocol deviations. Additionally, details of the surgical procedures are collected.

5.4.5. Visit 3 – 6 months (±30d) follow-up

At 6 months (±30d) after surgery the subjects will undergo the following assessments:

- **Oswestry Disability Index**
  - ODI will be collected as described in section 5.4.2.6.
- **Numeric Rating Scale Leg pain**
  - NRS leg pain will be collected as described in section 5.4.2.7.
- **Patient satisfaction**
  - Subjects will be asked if they are “satisfied”, “uncertain”, or “dissatisfied” with surgery outcome.

This visit can be performed over the phone.

5.4.6. Visit 4 – 12 months (±30d) follow-up.

At 12 months (±30d) after surgery the subjects will undergo the following assessments:

- **Flexion/extension X-rays**
  - Flexion/extension X-rays will be collected at the 12 month follow-up visit for all patients as described in section 5.4.2.5.
- **SPSI™ metric**

- The 12 month flexion-extension radiographs will be sent to MMI and the intervertebral motion will be analyzed using QMA® and the SPSI™ metric will be calculated. The 12 month SPSI™ metric will be used to document whether the decompression procedure changed the stability of the treated level in subjects who underwent decompression surgery only. Additionally, in subjects who underwent decompression and fusion surgery, the intervertebral rotation will be used to determine whether the fusion was successful at stopping motion between vertebrae. A level will be classified as fused if intervertebral rotation is < 2 degrees at the operated level and > 5 degrees at an adjacent level, and will be classified as not fused if rotation is ≥2 degrees[45]. It is expected that a proportion of patients will be considered indeterminate due to insufficient patient effort and those will not be included in the data analysis.

- **Oswestry Disability Index**
  - ODI will be collected as described in section 5.4.2.6.
- **Numeric Rating Scale Leg pain**
  - NRS leg pain will be collected as described in section 5.4.2.7.
- **Patient satisfaction**
  - Subjects will be asked if they are "satisfied", "uncertain", or "dissatisfied" with surgery outcome.
- **Assessment of any reoperations.**
  - The occurrence of any reoperations will be recorded along with the general type of reoperation (surgery at the originally treated levels or at the adjacent levels).
- **Analgesic use**
  - Current analgesic use of pain medication will be recorded at screening, 12 months and 24 months of the clinical investigation. Subjects will be asked of they use narcotic or non-narcotic pain relieving medication for their back problems, "yes regularly", "yes sometimes", or "no".
- **Assessment of adverse events**
  - Occurrence and assessment of all AEs will be recorded.

5.4.7. Visit 5 – 24 months (±30d) follow-up

At 24 months (±30d) after surgery the subjects undergo the following assessments:

- **Oswestry Disability Index**
  - ODI will be collected as described in section 5.4.2.6.
- **Numeric Rating Scale Leg pain**
  - NRS leg pain will be collected as described in section 5.4.2.7.
- **Patient satisfaction**
  - Subjects will be asked if they are "satisfied", "uncertain", or "dissatisfied" with surgery outcome.
- **Assessment of any reoperations.**
  - The occurrence of any reoperations will be recorded along with the general type of reoperation (surgery at the originally treated levels or at the adjacent levels).
- **Analgesic Use**

- Current analgesic use of pain medication will be recorded at screening, 12 months and 24 months of the clinical investigation. Subjects will be asked of they use narcotic or non-narcotic pain relieving medication for their back problems, “yes regularly”, “yes sometimes”, or “no”.

- **Assessment of adverse events**
  - Occurrence and assessment of all AEs will be recorded.

5.4.8. Activities Performed by Sponsor Representatives

The sponsor of the clinical investigation (Medical Metrics Diagnostics, Inc) will work with MMI to provide investigators, X-ray technicians, and subjects with training materials. MMI will also be responsible for managing transfer of flexion-extension radiographs from the clinical sites to MMI where the QMA and calculation of SPSI™ will be performed using previously validated methods. MMI will be responsible for getting the SPSI™ report to the clinical site and for addressing any difficulties that the investigators encounter with the SPSI™ reports.

5.5. Monitoring Plan

Monitoring will be performed by Factory-CRO for Medical Devices. Details of the monitoring activities are outlined in the Monitoring Plan.

6. STATISTICAL CONSIDERATIONS

Data analysis will be independently performed at MMDx and by a statistician independent of MMI. Discrepancies will be reviewed and resolved by the independent statistician. This will be done to reduce any potential errors.

6.1. Primary Endpoint

Proportion of surgical treatment plans changed after including SPSI™ metrics

The primary endpoint is the proportion of lumbar spinal stenosis treatment plans that change when SPSI™ results are used in establishing the surgical plan. The proportions will be analyzed using a statistical test for proportions. The hypothesis to be tested is that SPSI™ will result in a change in surgical plan for at least 15% of subjects.

Three lumbar spinal stenosis treatment plans (surgical plans) will be identified per the following table:

TABLE 3. DESCRIPTION OF SURGICAL PLANS

Surgical Plan	Description
P1	Pre-SPSI™ surgical plan
P2	Post-SPSI™ surgical plan
P3	Actual surgery performed

The primary endpoint will be investigated using the proportion of P2 surgical plans that changed relative to the P1 plan. This describes the proportion of surgical treatment plans that appeared to change by inclusion of the SPSI™ metric. The primary endpoint analyses will be done using the per-algorithm population, defined as enrolled subjects who received surgery, where the post- SPSI™ surgical plan is in accordance with the SPSI™ metric and who do not have any major protocol deviations.

6.1.1. Subgroup analysis related to primary endpoint

The data on changes to surgical plans will be further analyzed to better understand the changes as described below. This will be done for exploratory purposes and for planning subsequent research.

The comparison between the pre-SPSI™ surgical plan (P1), post-SPSI™ surgical plan (P2) and the actual surgery performed (P3) will be documented on a per-patient and per-level basis. With respect to the influence per-patient, the following table will be completed:

TABLE 4. SUBGROUP ANALYSIS OF THE EFFECTS OF CHANGES TO SURGICAL PLAN ON SURGERIES PERFORMED

Comparison	Proportion of Patients		
	No Change	Increased Levels Fused	Decreased Levels Fused
P2 versus P1			
P3 versus P2			

P3 versus P1			

6.2. Secondary Endpoint

Comparison of clinical outcomes in lumbar stenosis patients where surgical planning including SPSI™ compared to historical controls

After 12 month (± 30 days) the change from baseline (12 month minus PreOp) in both the ODI, and the region-specific NRS [46-48] leg pain score will be calculated for each subject in the study. These outcomes instruments have been used in many spine studies, are well-accepted, and there is reference data in the literature that can be used to help interpret results from the proposed study. ThesSecondary endpoint analyses will be done using the per-algorithm population. The per-algorithm population includes all patients where the surgeon modified the initial surgical plan as needed per the algorithm defined in Table 1.

The purpose of the ODI is "To indicate the extent to which a person's functional level is restricted by disability"[2]. The mean and standard deviation for the 12 month ODI, and the change in the 12 month ODI relative to baseline in study subjects will be compared (using a T-test) to the mean and standard deviations expected from peer-reviewed publications that have randomized lumbar stenosis patients to either decompression only or decompression and fusion. Most of this literature is already available at MMDx but an updated search will be completed using Google Scholar and pubmed prior to the data analysis so that any recent literature can be included. The data analysis will be repeated after 24 month outcomes have been collected.

The comparison of study data to historical control data can be done for each historical control study that has comparable data. The expected rate will be based on a review of the available literature. Many peer-reviewed publications do not report means and standard deviations in a manner that allows for use of their data directly as a historical control [4] although the data can nevertheless help to support choice of numbers to use. Table 5 summarizes some of the studies that provide historical control data.

Most of the prior literature reports a similar improvement in outcome scores for patients treated with decompression only versus decompression and fusion. The null hypothesis is that the use of SPSI™ report by investigators to select levels to treat and the type of surgery to use will NOT effect the improvement in clinical outcomes for lumbar stenosis patients treated with decompression only or decompression plus fusion. The null hypothesis would be rejected if, when SPSI™ is used to select treatment, the improvement in outcome scores is significantly better than reported in the peer-reviewed literature. Although it is unlikely that the sample size in the current study will be sufficient to address the null hypothesis with an acceptable significance level and statistical power, the data from this pilot study will be used to help establish sample sizes required to more definitively document the clinical benefit of SPSI™ for selecting levels and treatments in lumbar spinal stenosis patients.

TABLE 5: A SAMPLING OF PAPERS THAT PROVIDE POTENTIAL REFERENCE ODI AND NRS DATA. A MORE COMPLETE LIST WOULD BE GENERATED PRIOR TO INTERPRETING THE STUDY RESULTS BASED ON A COMPLETE LITERATURE

[2] https://eprovide.mapi-trust.org/instruments/oswestry-disability-index

REVIEW AND CONSULTATION WITH THE PARTICIPATING INVESTIGATORS TO ASSURE THAT THE HISTORICAL CONTROL DATA INCLUDE THOSE PUBLICATIONS THAT THE INVESTIGATOR USES TO INFORM PATIENTS ON EXPECTED OUTCOMES.

Study	FU Months	N	Delta ODI		Delta NRS Leg Pain	
			D	D&F	D	D&F
Weinstein 2010	24	109	-16.1(19.8)			
Austevoll	12	260/260	-17.5[16.1]	-19.7[18.3]	-3.0[2.9]	-3.5[2.8]
Ghogawala	12	35/31	-22.2[NR]	-26.1[NR]	NR	NR

Key to abbreviations in Table 5:

Delta ODI: The change in the Oswestry Disability Index at follow-up (FU) relative to PreOp.

Delta NRS Leg Pain: The change in the visual-analog score for patient reported leg pain.

D: Decompression surgery only

D&F: Decompression surgery and fusion surgery

6.3. Exploratory Endpoints

6.3.1. Exploratory research question 1: Association between preoperative SPSI™ and the facet fluid sign

The facet fluid sign is observation of an abnormally wide area of high signal intensity in the left and/or right facet joints. Prior research has demonstrated that SPSI™ (labeled QSI in the paper) is significantly elevated in the presence of the facet fluid sign [31]. Data from the current study will be analyzed for supporting or refuting evidence to the prior observation. However, due to the expense of image transfer and independent radiologist assessment of the MRI exams, the observations by the investigators will be used. Each investigator will be provided with training material on how to interpret the facet fluid sign. This training materials is based on training that was successfully used in the prior publication [31]. Analysis of variance tests (if data are normally distributed) or the Kruskal –Wallis equality-of-populations rank test will be used to test whether SPSI™ is significantly greater at levels identified by the investigators as having a facet fluid sign. This endpoint will be analyzed using the Safety Population.

6.3.2. Exploratory research question 2: Proportion of levels treated using decompression only that have an increase in SPSI™ at 12 months

As previously noted, one common justification for adding fusion surgery to surgery for decompression of lumbar stenosis, is that the decompression may create an instability that will later need to be treated. The fusion surgery is sometimes used prophylactically against the possibility of developing instability following decompression surgery. However, if instability rarely develops, this justification is not appropriate. Multiple research studies have been published providing data on the low-proportion of patients that develop instability following decompression-only surgery [7, 40, 49-54]. However, it is somewhat difficult to fully accept those studies since there are also scientific reviews concluding that there is currently no validated method for diagnosing instability [13]. Therefore, the proportion of patients where SPSI™

increases significantly following decompression-only surgery will be determined using an objective metric for spinal stability. This analysis will be completed as simple descriptive statistics and also using a simple test of proportions in comparison to the proportion of patients reported in prior publications. There is some evidence that a high translation-per-degree-of rotation can be associated with low-back symptoms [19]. In addition, there is some evidence that increased spondylolisthesis following decompression may be associated with worse outcomes [55, 56], so a binary classification (significantly increased SPSI™ versus no change in SPSI™) will be analyzed as a covariate when analyzing clinical outcome scores. If the change in SPSI™ is greater than +0.75, then that patient will be classified as having increased SPSI™. Otherwise, the patient will be classified as having no significant change. This endpoint will be analyzed using the Per-algorithm Population.

6.3.3. Exploratory research question 3: Reoperation rate at 1 and 2 years following surgery

To provide confidence that clinical results of the current study are consistent with previously published data, the occurrence of any reoperations will be recorded along with the general type of reoperation (surgery at the originally treated levels or at the adjacent levels). Some reoperations would be expected based on previously published data (for example Bydon et al [57]). This endpoint will be analyzed using the Per-algorithm Population.

6.3.4. Exploratory research question 4: Dependence of outcomes on non-union of levels treated using fusion surgery

The clinical outcomes following surgical treatment of lumbar spinal stenosis can depend on multiple factors. It can be difficult to determine the true effect of a specific surgical procedure on clinical outcomes, without reliably accounting for the cofactors that may affect outcomes. Unfortunately, there are limited data available to determine how best to account for cofactors. Although not all published data are consistent, there is evidence that fusion surgeries where the surgery fails to stop motion between vertebrae may have worse outcomes than in patients where the fusion surgery stops motion between vertebrae. For this reason, per-protocol flexion-extension radiographs will be obtained at 12 months for those patients treated with decompression plus fusion surgery. The flexion-extension radiographs will then be used to calculate intervertebral rotation at the treated level. If the rotation is greater than 2 degrees, then that level will be classified as a non-union. This threshold of motion has been used in multiple prior studies, so some reference data are available. It is likely that a much larger sample size would likely be required to rigorously assess this cofactor, so this exploratory endpoint is not being used to power the current study. This endpoint will be analyzed using the Per-algorithm Population.

6.4. Safety endpoint

An overall summary of AEs will be provided including the number of events and percent of subjects with any AEs, SAEs, and USADEs. For each type of event, the number of events and number and percent of subjects with the event will be provided in a table. Separate summaries of all adverse events will be summarized by relationship to device and procedure. The safety endpoint will be analyzed using the safety population.

6.5. Sample Size

The primary endpoint will be investigated using the proportion of surgical plans recorded after integrating SPSI™ metrics that changed relative to the surgical plan recorded prior to accessing the SPSI™ metrics. Since all of the investigators will have extensive experience with the surgical treatment of lumbar spinal stenosis patients, it is reasonable to assume that each individual surgeon would consistently generate the same treatment plan if they managed the same patient at multiple visits. published data was found documenting this assumption, but the clinicians tend to agree with that assumption.

Nevertheless, we will allow for the possibility that 10% of treatment plans could differ if surgeons were to generate treatment plans at multiple visits. Further, we will assume that for the SPSI™ metrics to be accepted as clinically effective, then at least 15% of treatment plans would need to be changed by inclusion of SPSI™ metrics. With alpha = 5% and power = 90%, a simple test of proportions indicates that a sample size of 59 patients would be required to determine if the proportion of treatment plans changed after including SPSI™ metrics was at least 25% assuming that 10% of treatment plans could change due to variability in how surgeons establish treatment plans (Stata/IC ver 15, StatCorp, College Station, TX).

To allow for up to 6 subjects that need to be dropped from the analysis for various reasons, 65 subjects are required to be included to assure at least 59 subjects are available in the final data analysis.

Additionally, the sample size requirement assumes that the investigators will follow any changes in surgical plan that the SPSI™ metrics would support. Since investigators can choose to reject the changes supported by the SPSI™ metrics, additional subjects may be recruited. Based on the estimation that in a maximum of about 25% (65 x 25% = 17) of the cases, the SPSI™ metric will not be followed, up to 80 subjects may be recruited in the study to ensure that there are 65 included subjects who received surgery and where the post- SPSI™ surgical plan is in accordance with the SPSI™ metric.

Each clinical site contributing to the study must aim to enroll at least 20 patients.

6.6. Analysis Populations

Data analysis with respect to the primary and secondary endpoints will be completed for two defined populations:

1. Safety Population: Enrolled subjects who received surgery, regardless of whether the investigator changed the surgical plan to conform with the results of the SPSI™ metrics.
2. Per-algorithm Population: Enrolled subjects who received surgery, where the post- SPSI™ surgical plan is in accordance with the SPSI™ metric and who do not have any major protocol deviations.

6.7. Missing Data

No imputation or adjustments for missing data will be performed. All available data will be analyzed per the defined analysis populations.

6.8. Stopping Rules

The proportion of surgical treatment plans that changed after including SPSI™ metrics will be monitored throughout the clinical investigation. If it becomes clear that the proportion of changed reports is so low that the data are unlikely to support the value of SPSI™ in surgical treatment planning, then the study may be stopped early. This decision would be made in consultation with the Principal Investigators to assure

that they agree with the conclusion that the SPSI™ reports are proving to be of no or only very limited value in surgical treatment planning.

6.9. Interim analysis

An interim analysis will be performed after the last subject has completed the surgery visit.

7. DATA MANAGEMENT

7.1. Data Review, Database Cleaning and Issuing and Resolving Data Queries

An electronic data capture (EDC) system with eCRFs (electronic CRF) will be used for this study. The data entered into the EDC will be fully validated, using study-specific range and consistency checks and database listings. Queries will be issued to the site via the EDC system, and are to be resolved by the investigator or his designee using the EDC system. An audit trail is available for tracking all information that the EDC user enters, modifies or deletes.

7.2. Source Data requirements

The Investigator or its delegate will perform primary data collection drawn from original documents (printed, optical or electronic document containing source data). Data to be collected for study purposes must not be entered directly into the eCRF before being recorded first in the source documents. All source documentation must be available for review by the study monitor during monitor visits. Source data is defined as all information in original records, certified copies of original records of clinical findings, observations, or other activities in a clinical investigation, necessary for the reconstruction and evaluation of the clinical investigation

7.3. Procedures for verification, validation and securing of electronic clinical data Systems

Data validation will be completed on a regular basis. The entire database will be re-validated to ensure that there are no outstanding data discrepancies, prior to database lock. Any changes to the database after that time will require written agreement by MMDx.

7.4. Case Report Forms

The investigators shall ensure the accuracy, completeness, legibility and timelines of the data reported in eCRFs and in all required documentation. Data reported on the eCRF shall be supported by the source documents with any discrepancies being explained. Any corrections made to documents shall be done according to ISO 14155 guidelines. If an item is not available or is not applicable, this fact should be indicated; no space is to be left blank. The investigator who has signed the protocol signature page or his/her authorized designee is to personally sign the eCRFs to validate that the observations and findings are recorded on the eCRFs correctly and completely. The eCRFs are to be completed in a timely manner after the patient's visit. Failure to meet the documentation requirements may lead to the disqualification of an investigator.

7.5. Data Retention

The investigator maintains all study records for 15 years. Records to be retained may include: all correspondence, documentation of device receipt and disposition, each subject's case history and record of exposure to the device, the protocol and amendments, Investigator Brochure, and dates and reasons for any protocol deviations or as otherwise specified by the applicable laws and regulations.

7.6. Subject Confidentiality

Subject confidentiality will be maintained throughout the clinical study in a way that ensures the information can always be tracked back to the source data. For this purpose, a unique subject identification code will be used that allows identification of all data reported for each subject. Data relating to the study might be made available to third parties (for example in case of an audit performed by regulatory authorities) provided the data are treated confidential and that the subject's privacy is guaranteed.

Informed consent and other documentation in accordance with the relevant country and local privacy requirements (where applicable) are to be obtained from each subject prior to enrollment into the study, in accordance with the applicable privacy requirements.

7.7. Other Aspects of Clinical Quality Assurance

The clinical investigation will be conducted and monitored by Factory CRO under the sponsorship of MMDx. The sponsor, or the sponsor's representative, may conduct audits at the investigational sites. Audits may include, but are not limited to, device supply, presence of required documents, the informed consent process, and comparison of CRFs with source documents. The investigator agrees to participate with audits conducted at a reasonable time, in a reasonable manner.

8. PROTOCOL AMENDMENTS

Investigators may not modify this protocol without obtaining written concurrence of the sponsor and the Ethics Committee and Competent Authority when required.

9. PROTOCOL DEVIATIONS

The investigator agrees to conduct the investigation in accordance with this protocol. An investigator may not deviate from this protocol without first receiving approval in writing from the sponsor and Ethics Committee, except when necessary to eliminate apparent immediate hazards to a subject.

Deviations will be documented on CRFs. Investigators will also adhere to procedures for reporting investigation deviations to their ethical committee in accordance with their specific reporting policies and procedures.

Protocol deviations to the in/exclusion criteria and deviations that affect the primary endpoints are considered major protocol deviations. Other deviations are considered minor protocol deviations. All deviations will be reviewed by the sponsor. The sponsor is responsible for major/minor classification of the deviations.

Any deviations from this protocol undertaken to protect the life or physical well-being of a subject in an emergency situation must be reported to MMDx within 24 hours of occurrence and to the respective Ethics Committee as soon as possible, but in no event later than five calendar days after the emergency occurs.

9.1. Corrective and Preventive Actions

MMDx or its representatives will evaluate protocol deviations during monitoring visits. Individual event corrective and preventive actions may be recommended at that time. In addition, deviations occurring across investigational sites will be reviewed by MMDx on a periodic basis to determine if more global preventive actions may be required.

9.2. Investigator Disqualification Criteria

MMDx reserves the right to terminate an investigator/investigational site for any of the following reasons:

- Failure to secure subject informed consent including protection of personal data prior to enrollment.
- Failure to report safety events within 24 hours of discovery (to MMDx) after learning of the event.
- Failure to report serious adverse device effects within 24 hours of discovery.
- Repeated investigational plan deviations.
- Repeated failure to appropriately complete case report forms.
- Failure to enroll an adequate number of subjects.
- Loss of or unaccounted for investigational product inventory

10. DEVICE ACCOUNTABILITY

The SPSI™ reports will be generated for each subject, preoperatively and at 12 months following surgery. A study-specific identification number will be assigned to each subject upon enrollment into the study. The study specific identification number will include the site identification number and the subject number in sequential order as enrolled at the site. All SPSI™ reports will use the subject identification number and the radiograph acquisition date.

11. STATEMENTS OF COMPLIANCE

This clinical investigation will be conducted in compliance with the principles that have their origin in the latest version of the Declaration of Helsinki, this clinical investigation plan, requirements of the approving ethics committee and competent authorities, ISO 14155, Medical Devices Directive 93/42/EEC Annex X – Clinical Evaluation, and other applicable regulatory requirements whichever provides the greater protection of the individual.

This clinical investigation will not be initiated until approval has been obtained from the ethics committee and the regulating competent authority. Any additional requirements imposed by the ethics committee or regulatory authority will be followed. No deviation from the protocol will be implemented without the prior review and approval of the ethics committee except where it may be necessary to eliminate an immediate hazard to a subject. In such case, the deviation will be reported to the ethics committee as soon as possible.

Clinical trial insurance will be secured prior to investigation initiation.

12. INFORMED CONSENT PROCESS

The investigator is responsible for assuring that written informed consent is obtained from each patient prior to participation in the clinical investigation. Should the investigator delegate the responsibility of conducting the informed consent process to a designee, the investigator must ensure and document appropriate training of the authorized designee.

The investigator will use an Ethics Committee approved informed consent form in the native language of the country that was prepared in accordance with this protocol, ISO 14155 and relevant regulatory requirements.

While an investigator may discuss availability of the investigation with a prospective patient without first obtaining consent, informed consent must always be obtained from a patient prior to initiation of any clinical procedures dictated by the protocol that are performed solely for the purpose of determining eligibility to participate in the clinical investigation.

Patients must be fully counseled and informed of their options, risks and benefits, and should have every opportunity to ask questions about participation in the investigation. This process includes a thorough explanation of the information letter and informed consent form that the patient will be asked to sign acknowledging that they understand and desire to participate in the investigation. A copy of the informed consent document will be given to the participants for their records. Patients may withdraw consent at any time throughout the course of the clinical investigation, without any consequences for their further care and without the need to justify their withdrawal decision.

If new information regarding the investigational device becomes available and/or the protocol changes and this information can significantly affect a subject's future health and medical care, subjects will be informed of the information and may be asked to sign a revised informed consent form.

13. ADVERSE EVENTS, ADVERSE DEVICE EFFECTS AND DEVICE DEFICIENCIES

13.1. Definitions

13.1.1. Adverse Events

An adverse event is 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. This definition includes events related to the investigational medical device or the comparator; events related to the procedures involved and for users or other persons, this definition is restricted to events related to investigational medical devices.

Note: Adverse event reporting will start at the time of the surgery. Adverse events that occur between the signing of the informed consent and the initiation of the surgery will thus not be reported on the CRFs. Underlying diseases are not reported as adverse events, but any deterioration in severity will be reported. Normal post-operative complications as a result of the surgery (e.g. pain, wound leakage) are not considered AEs. Excessive, outside normally expected range complications should be considered as AE as determined by the Investigator.

13.1.2. Adverse Device Effect

An adverse device effect is an adverse event related to the use of an investigational medical device. 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. And this definition includes any event resulting from use error or from intentional misuse of the investigational medical device.

13.1.3. Device Deficiency

A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. Device deficiencies include malfunctions, use errors, and inadequate labelling.

13.1.4. Serious Adverse Event

A serious adverse event is 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

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.

13.1.5. Serious Adverse Device Effect

A serious adverse device effect is an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

13.1.6. Unanticipated Serious Adverse Device Effect

An unanticipated serious adverse device effect is a 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.

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.

13.1.7. Device Relatedness

Each SAE will be classified according to five different levels of causality. The sponsor and the investigators will use the following definitions to assess the relationship of the serious adverse event to the investigational medical device or procedures.

Not related: relationship to the device or procedures can be excluded when:

- the event is not a known side effect[3] 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[4], when applicable;

[3] When the event is not a known side effect of the product category the device belongs to or of similar devices and procedures, generally is considered “not related”. Yet, the unexpected effect shall not be excluded from evaluation and reporting.

[4] If an investigational device gives an incorrect diagnosis, the patient might, for example, receive an unnecessary treatment and incur all the risks that accompany that treatment, or might be incorrectly diagnosed with a serious disease. In other cases, the patient might not receive an effective treatment (thereby missing out on the benefits that treatment would confer), or might not be diagnosed with the correct disease or condition.

- 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.

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.

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.

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.

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.

The sponsor and the investigators will distinguish between the serious adverse events related to the investigational device and those related to the procedures (any procedure specific to the clinical investigation). An adverse event can be related both to procedures and the investigational device. Complications of procedures are considered not related if the said procedures would have been applied to the patients also in the absence of investigational device use/application.

AEs occurring as a result of the decompression or decompression and fusion surgery will be considered procedure related.

13.1.8. Severity

The severity of the event will be classified based on the following definitions:

- Mild: Awareness of signs or symptoms, but easily tolerated and are of minor irritant type causing no loss of time from normal activities. Symptoms do not require therapy or a medical evaluation; signs and symptoms are transient.
- Moderate: Events introduce a low level of inconvenience or concern to the participant and may interfere with daily activities, but are usually improved by simple therapeutic measures; moderate experiences may cause some interference with functioning.
- Severe: Events interrupt the participant's normal daily activities and generally require systemic drug therapy or other treatment; they are usually incapacitating.

13.2. Reporting Requirements

13.2.1. Time Lines for Reporting

All serious adverse events must be reported by the principal investigator to the sponsor or delegate as soon as possible, but in any case, within 24 hours of being aware of the event. SAEs should be reported using iDatafax or via email to:

Factory CRO for Medical Devices
Email address: datafax@factory-cro.com
Phone number: +31 30 229 2727
Fax number: +31 30 228 7542

13.2.2. Reporting Adverse Events

Adverse event information will be collected on all subjects. At every subject visit, the investigator will determine if there has been an adverse event since the last visit. All adverse events must be reported on the Adverse Event CRF. The date of the initial event, treatment and resolution will be documented. Adverse events will be evaluated and differentiated by:

- Seriousness of the event
- Causality of the event (in relation to the device or procedure)
- Severity of the event

13.2.3. Foreseeable Adverse Events and Anticipated Adverse Device Effects

Anticipated Adverse Device Effects are described in section 3.2.

13.2.4. Reporting Device Deficiencies

All device deficiencies observed during the course of the clinical investigation shall be documented in the Device Deficiency CRF and if applicable, on the Adverse Event CRF.

13.2.5. Reporting Serious Adverse Events and Serious Adverse Device Effects

In the Netherlands SAEs will be reported by the sponsor (or its representative Factory CRO for Medical Devices) to the accredited Ethics Committee that approved the protocol and Competent Authority.

Reporting Timelines to the Ethics Committee:

The Ethics Committee requires that all SAEs occurring in all participating sites in the Netherlands and all foreign countries will be reported. The timelines and reporting requirements are as follows:

1. An SAE which indicates an imminent risk of death, serious injury, or serious illness and that requires prompt remedial action for other patients/subjects, users or other persons or a new finding to it: immediately, but not later than 7 calendar days after awareness by sponsor of a new reportable event or of new information in relation with an already reported event.
2. All other SAEs will be reported within 15 calendar days.

Reporting to the Ethics Committee will occur by completing the SAE form in the ToetsingOnline portal (https://toetstingonline.ccmo.nl). These SAEs are automatically forwarded to the Ethics Committee.

Reporting Timelines to the Competent Authority in the Netherlands (IGJ):

IGJ requires that all SAEs (device-related and not device-related) occurring in all participating sites in all participating countries will be reported.

The reporting timelines are as follows:

1. An SAE which indicates an imminent risk of death, serious injury, or serious illness and that requires prompt remedial action for other patients/subjects, users or other persons or a new finding to it: Immediately, but not later than 2 calendar days after awareness by sponsor of a new reportable event or of new information in relation with an already reported event.
2. All other SAEs will be reported quarterly using SAE line listing according the reporting table of MEDDEV 2.7/3 SAE reporting guidelines.

All SAEs can be reported via email: meldpunt@igj.nl

13.3. Medical Monitor

A medical monitor, who is an independent physician not participating as a clinical investigator in the clinical investigation, will provide ongoing medical monitoring of incoming safety study data during the study conduct.Details of the medical monitor responsibilitiesare included in the Safety Data Handling Plan and include:

- Maintaining ongoing assessment of the safety profile of the investigational device during the investigation.

  Provide medical surveillance and evaluation of Serious Adverse Events (SAEs).

13.4. Data Monitoring Committee

A Data Monitoring Committee will not be established for this clinical investigation.

14. VULNERABLE POPULATION

No vulnerable population will be included in this clinical investigation.

15. SUSPENSION OR PREMATURE TERMINATION OF THE CLINICAL INVESTIGATION

MMDx reserves the right to terminate to suspend or prematurely terminate the clinical investigation if there is sufficient reasonable cause. Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of performance metrics that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Device deficiency or malfunction
- Product limitation

MMDx reserves also the right to terminate an investigator/investigational site for any of the reasons provided in Section 9.2: Investigator Disqualification Criteria. MMDx will justify its decision in writing and promptly notify the investigators, Ethics Committees and Competent Authorities.

In case of study termination or suspension, the investigators must inform the patients and may inform the personal physician of the patients to ensure appropriate care and follow-up is provided. In the case of a study suspension, patient enrollment must stop until the suspension is lifted.

In the case of a study suspension or premature termination of the study, enrolled subjects should continue to be followed out of consideration of their safety for 30 days after study termination or considered clinically stable.

16. PUBLICATION POLICY

16.1. Publication by Medical Metrics Diagnostics, Inc.

After study closure, the results of this clinical investigation will be summarized in a Clinical Study Report, which will be submitted to the investigators, Ethics Committees and appropriate regulatory authorities. This report will include a summary of the study results based on a statistical evaluation and clinical assessment.

16.2. Publication by Investigational Sites

The conditions under which an investigator may publish results from this clinical investigation in any form are defined in detail in the clinical trial agreement.

17. BIBLIOGRAPHY

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