Official Title: Feasibility of Bridge for Post-Operative Pain Management in Hip Arthroplasty

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Feasibility of Bridge for Post-Operative Pain Management in Hip Arthroplasty

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Study Devices: Masimo Bridge

Sponsor Protocol Number: CHEL0001

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1 INTRODUCTION

This document is a clinical investigational plan for a human research study. The study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. By participating in the study, the Investigator agrees to adhere to all stipulations of this protocol, the conditions of IRB approval, federal and local regulatory requirements, 21 CFR 812, ISO-14155 and International Conference on Harmonization Good Clinical Practice guidance ICH GCP.

1.1 Background and Rationale

The aim of the current project is to investigate the effectiveness of Auricular Percutaneous Electrical Nerve Field Stimulation (PENFS) device in the management of post-operative pain following hip arthroplasty. In 2020, an estimated 498,000 primary total hip arthroplasties are expected to be performed in the US and forecast to grow by over 30% in the next 5 years driven by significant gains in quality of life post joint replacement, an aging population, and an obesity epidemic with increasing osteoarthritis (OA) incidences [1]. Despite the availability of non-opioid treatments for postoperative pain following THA, approximately 90% of patients were still prescribed opioids within 60 days from discharge [2]. Postoperative pain can have a negative effect on patient tolerance of rehabilitation exercises, which is important to help return to normal functioning. As compared to the present use of opioids for perioperative pain management, the use of a complementary, non-pharmacologic approach offers the advantage of analgesia without the associated side effect and eliminating the potential risk of opioid addiction stemming from exposure to the drug. If effective, this alternative approach may revolutionize post-operative pain management and have a substantial impact on health care costs and morbidity.

Masimo Corporation develops technologies that help reduce the risks associated with prescribed opioids, such as overdoses and opioid use disorder. In particular, opioid use disorder is a serious public health issue that negatively impacts many communities around the world, and the current opioid epidemic has led to a renewed interest in exploring non-pharmacological techniques to treat post-operative pain. In the United States, over $600 billion is spent every year on opioid addiction, including $79 billion related to opioid addiction following surgery. Furthermore, an increasing number of patients are suffering from other known adverse effects of opioid use following surgery, including post-operative nausea and vomiting, respiratory depression, immunosuppression, and constipation.

Despite many initiatives to decrease the use of opiates in the perioperative setting, opioids continue to be regularly prescribed before, during and after surgery. Although the risk of opioid addiction following surgery is recognized, the percentage of patients who develop an opioid use disorder following surgery is not well understood. To date, there has been virtually no agreement regarding the duration and dosage that qualify for opioid dependence following surgery, nor that a clear estimation of the factors such as biological, psychosocial and socioeconomic that increase the risk of using opioids for extended periods of time after surgery. Therefore, in order to combat this growing health crisis at the ground level, it is incumbent upon the medical community to explore alternative methods of pain control to treat the surgical population in order to change the incidence of post-operative opioid addiction.

Percutaneous Nerve Field Stimulation (PNFS) is one of these recognized methods that ongoing research has shown to be effective as a complementary method of pain management. While PNFS is not a novel concept, clinical indications of auricular field stimulation have been limited in the past due to requirement of bulky, stationary and non-disposable stimulators and electrodes. These technological limitations made it difficult to establish the real clinical potential of auricular stimulation for the perioperative management of pain in surgical patients, despite the demonstration that auriculotherapy has been shown to relieve pain in the postoperative setting.

Bridge™ is a battery operated and disposable Auricular Percutaneous Electrical Nerve Field Stimulation (PENFS) device that is FDA cleared for the treatment of symptoms related to opioid withdrawal, conditions that include pain and nausea and

vomiting, which also happen to occur in patients following surgery. Furthermore, preliminary data suggests that the Bridge device may be useful in controlling perioperative opioid consumption and pain following kidney donor surgery [3]. The novelty of the Bridge device is in its use of alternating currents of stimulation over a large field and with higher voltage in order to influence central pain areas. Specifically, the device stimulates branches of Cranial Nerves V, VII, IX and X, and the occipital nerves, identified by transillumination. Such stimulation is transmitted to the nucleus of these cranial nerves which interact with a number of other nucleus located at the level of of the central nervous system, the limbic system, and the ascendant and descendant pain pathway. This allows the modulation of stress, anxiety and pain through the interaction, for example, of the nuclei of the amygdala (structure involved in the response to fear and anxiety), the thalamus (structure involved in the management of visceral and somatic pain, and addiction), and tractus solitarie (structure involved in the control of blood pressure). The stimulation of these nuclei produces a modulation of the pain impulses from the visceral and/or somatic structures to supraspinal areas; and a reduction in anxiety and control of blood pressure and heart rate associated with the sympathetic and parasympathetic nervous system.

2 STUDY DEVICES

2.1 Bridge (active) vs. Sham device

Bridge is a device that electrically stimulates branches of Cranial Nerves V, VII, IX and X, and the occipital nerves identified by transillumination through percutaneous electrodes.

The components of the Bridge device include the following:

- Percutaneous electrical nerve field stimulator (PENFS) system
- Multi-pin wire harness percutaneous electrode
- Pen light for use in the transillumination technique that aids in positioning of the percutaneous electrodes

The wire harness percutaneous electrode array consists of 4 leads. The 1-1-1-4 configuration consists of three single-needle leads, and one 4-needle array. The stimulator is placed behind the ear and percutaneous electrodes are positioned utilizing the transillumination function of the device. The transillumination technique assists in the visualization of neuro-vasculator matrixes, to aid in the placement of the percutaneous electrodes near the nerve branches in the ear. The Bridge device has a 120 hour run-time and has a pulse sequence of 2 hours on and 1 minute off with the cycle repeating over the 120 hour run-time.

The sham device has the same appearance and will require the same placement technique as the Bridge (active) device but will not deliver electrical impulses.

2.2 Device Accountability

2.2.1 Receipt of Study Devices

Masimo may ship or hand-carry devices and study supplies to the investigative site. Upon receipt of the of the study device and supplies, an inventory must be performed and the Equipment Shipment Check Form (FRM-2713) and the Device Accountability Log (FRM-3407) will be completed for each device and signed by the receiver. It is important that the designated study staff counts and verifies that the shipment contains all the items noted in the shipment inventory. Any damaged or unusable study devices in a given shipment will be documented in the study files. The investigator must notify the study sponsor of any damaged or unusable study devices that were supplied to the investigator's site.

2.2.2 Use of Study Device

Use of devices will be documented on case report forms (CRF) for each subject. Any unused devices must be returned to the Sponsor at the end of the study or before product expiration date.

2.2.3 Return or Destruction of Study Device

At the completion of the study, there will be a final reconciliation of study devices. This reconciliation will be logged on the device accountability log. Any discrepancies noted will be investigated, resolved, and documented prior to return or destruction of unused study devices. Devices destroyed on site will only be upon written instruction from the Sponsor and will be documented in the study files.

2.3 Risk/Benefits

Benefits: There may be direct benefits to the enrolled subjects. The Bridge device may be used as an aid to reduce post-operative pain symptoms if they receive the active device. There are no anticipated benefits to subjects who receive the sham device.

Device risks: The Bridge device is to be operated by, or under the supervision of, qualified personnel only. Read the manual, directions for use, all precautionary information, and specifications before use. Refer to the Operator's Manual for safety information, warnings, and cautions.

- The device is contraindicated for use by patients with cardiac pacemakers, hemophilia and psoriasis vulgaris.
- The device should only be applied to healthy, clean, intact skin.
- The device therapy is limited to 120 hours, after which the device is disposable.
- The appliance is splash-proof but not water tight. When showering, the device must not be allowed to come into direct contact with water.
- The device is also contraindicated for use in patients with a previous history of sensitivity to compound benzoin tincture, which is used to attach the elecrodes to the ear.

3 STUDY OBJECTIVES

The aim of this research is to gather data regarding the feasibility of the Bridge system for the management of pain following total hip arthroplasty (THA; a.k.a. total hip replacement).

4 STUDY DESIGN

This is a prospective, randomized, blinded, sham-controlled study design in up to 60 subjects. Individuals scheduled for primary total hip arthroplasty will be approached and consented for the trial. Patients undergoing primary unilateral total

hip surgery will be expected to be discharged on the day of surgery, or the next day but no later than 48 hrs following surgery. The anticipated duration of subject participation in this study will be approximately 1 month.

4.1 Study Arms

4.1.1 Treatment Arm

Bridge auricular therapy will be given in addition to standard of care. Research coordinators that have been trained in placing the Bridge device will apply the device in the immediate post-operative setting (post-anesthesia care unit, PACU). The device will be attached according to the instructions for use provided. Pain scores using a numerical scale will be collected at rest and movement, as well as total opioid consumption and the device tolerability. [redacted]

4.1.2 Control Arm

Same treatment as in the active arm with the only exception being the use of a sham Bridge device. The sham Bridge device will be identical in appearance to the active device but will have no electrical current and no electrode needles.

4.2 Study Endpoints

The study endpoints are designed to evaluate the impact of Bridge on pain scores and amount of opioids consumed.

4.2.1 Primary Endpoints

The primary study endpoints are the change in pain scores and opioid consumption from the day of surgery through post-operative day 5 between sham and active groups.

4.2.2 Secondary Endpoints

Secondary end points will include opioid consumption from the day of surgery to 30 days post-op, daily changes in pain using the Numeric Rating Scale (NRS) on a scale 0-10 from the day of surgery through post-operative day 30, incidence of post-operative nausea and vomiting (PONV), time to oral intake, time to ambulation, time to discharge from the recovery room, time to discharge from the hospital, and the tolerability of the device using a numeric scale from 1-10 obtained via a follow up phone call 5 days after the surgery.

5 CLINICAL TEST SITE

[redacted]

Site 2:

[redacted]

6 SUBJECT SELECTION AND WITHDRAWAL

6.1 Number of Subjects

Up to 60 subjects will be enrolled in this study with a potential interim review of the data after 30 patients.

6.2 Inclusion Criteria

- Subject is 18 years of age or older
- Subject scheduled for elective primary unilateral total hip arthroplasty (THA)
- Subject opioid use is less than 60 milligram morphine equivalent for the last 30 days
- Subject has given written informed consent to participate in the study

6.3 Exclusion Criteria

- Subjects with a PROMIS Anxiety raw score of >19
- Subjects who are pregnant or breastfeeding
- Subjects with cardiac pacemakers or other implanted devices (e.g. vagal nerve simulators)
- Subjects with hemophilia
- Subjects with Psoriasis vulgaris
- Subjects with a history of active depression, anxiety or catastrophizing
- Subjects with active alcoholism or drug abuse
- Subjects with severe chronic pain condition that requires daily preoperative opioid dependence
- Subjects deemed not suitable for the study at the discretion of the principal investigator
- Subjects who are concurrently participating in any other research study

6.4 Study Timelines

Each individual subject will actively participate for the duration of approximately 5 days. There will be a follow-up phone interview at POD 7 and POD 30. This study is anticipated to require up to 6 months for completion of patient enrollment.

6.5 Subject Status

Subjects will be classified according to the following statuses:

- Screened – all subjects who met inclusion criteria per chart review and approached for consent.
- Enrolled – all subjects who went through the informed consent process and signed the informed consent form.

- Screen Failure – subjects who do not meet all eligibility criteria after giving informed consent. Upon determination that the subject does not meet all eligibility criteria, the reason for the subject's ineligibility will be documented on the Screening and Enrollment Log.
- Completed – subjects who wear the Bridge device for 120 hours, and complete all assements through post-operative day 5.
- Withdrawn – subjects who do not complete study either because they voluntarily choose not to participate further in the study and withdraw their consent, or they are discontinued from the study per PI discretion.
- Lost to Follow-up – subjects who are unreachable for assessments during the 1 week and/or 1 month post-operative follow-up. This includes subjects who completed study or were withdrawn from the study but did not withdraw their consent. Subjects will be classified as lost to follow-up if study staff is not able to reach them after three attempts.

6.6 Subject Withdrawal

All enrolled subjects have the right to withdraw their consent at any time during this study. All data collected until the time of subject withdrawal will remain in the study database and will be used for analysis. If a subject is withdrawn from the study, the reason for withdrawal will be recorded on the CRF.

6.7 Subject Discontinuation by Investigator

An Investigator may discontinue a subject from the study, with or without the subject's consent for any reason that may, in the Investigator's opinion, negatively affect the well-being of the subject, subject non-compliance, or if the IRB stops the study for any reason. If a subject is discontinued from the study, the Investigator will promptly inform the subject. The reason for discontinuation will be recorded on the CRF.

7 STUDY PROCEDURES

7.1 Subject Recruitment and Pre-Screening

Persons scheduled for elective total hip arthroplasty will be approached and screened by a Principal Investigator, nurse or research staff for suitability for this study. Persons who meet all of the inclusion and none of the exclusion criteria will be asked if they are interested in participating in the study. A subject is considered enrolled in the study once the subject's written informed consent has been documented. Consent may be obtained pre-surgery.

If the subject signs the Informed Consent form and is identified later as failing to meet all eligibility criteria, the subject will be classified as a screen failure. Upon determination that the subject does not meet all eligibility criteria, the reason for the subject's ineligibility will be documented on the Screening and Enrollment Log for the study. In the event that a subject leaves the study prematurely or is withdrawn from the study, another subject may be recruited.

A partial waiver of HIPAA authorization is being requested for the pre-screening process for this study. The pre-sreening process would require study personnel to access personal health information to identify prospective subjects without HIPAA authorization, and this would occur prior to introducing them to the study or obtaining informed consent. Informed consent and HIPAA authorization will be obtained for all patients who are interested in participation; however, the pre-screening process would require a partial waiver of HIPAA authorization, as the research study could not be practicably carried out without this partial waiver of authorization. The participants' rights and welfare are not adversely affected by the waiver. Patients' protected health information (PHI) will not be inappropriately reused or disclosed to any other person or entity. To further safeguard all protected health information, the data collected for the purposes of this study will not be labeled with any personal identifying information, or with a code that can be linked to personal identifying information. The data will not be stored with any protected health information identifiers.

7.2 Informed Consent Process

The Investigator(s) and/or staff delegated for this task are responsible for conducting the informed consent process and for obtaining written informed consent and the HIPAA/data protection authorization from each potential subject before any study-specific procedures required by the clinical protocol are performed. The Investigator shall not allow subjects to participate in the study or consent any subjects prior to receiving IRB approval of the consent process.

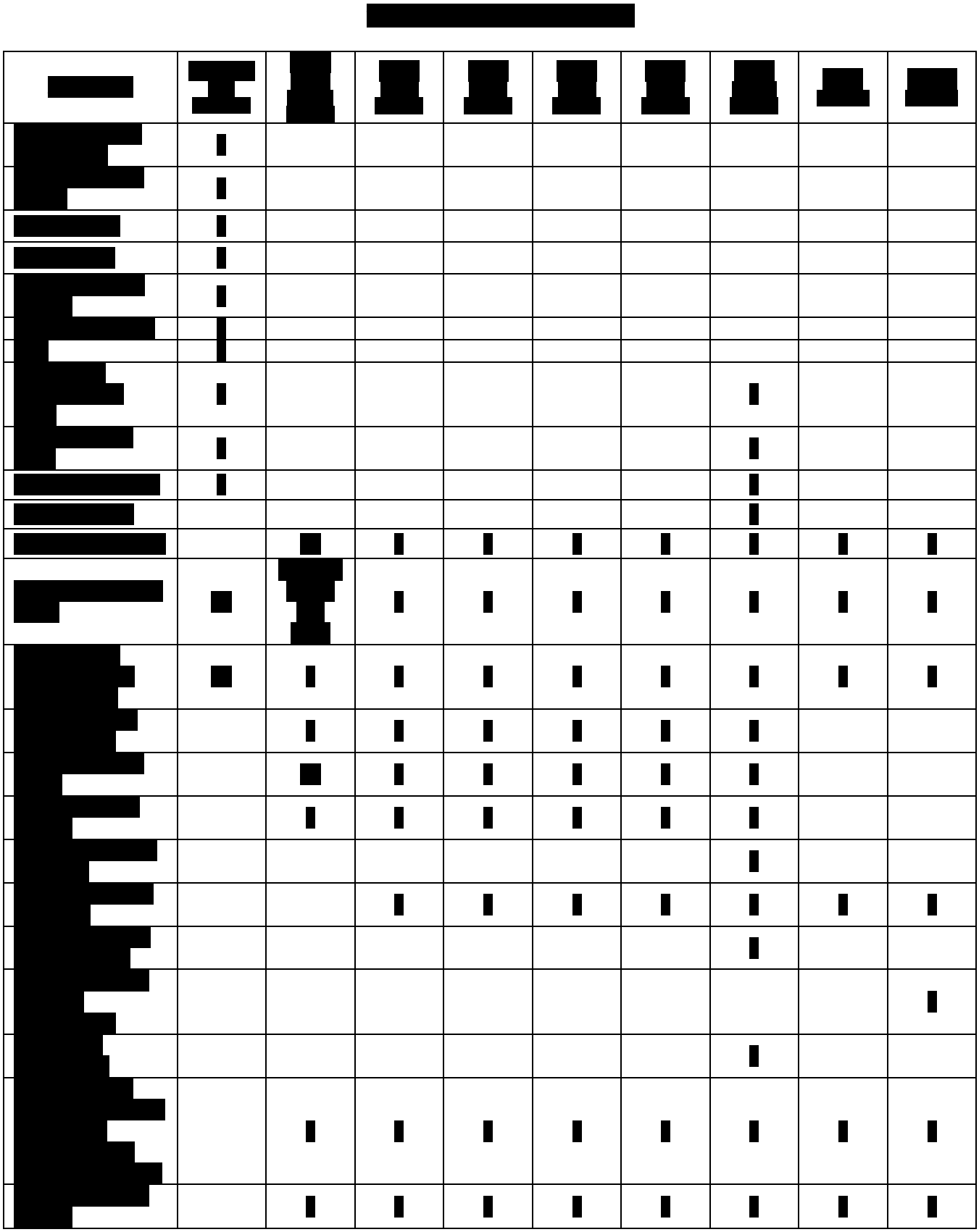
Informed consent should be obtained in written format and using a form approved by the local IRB and Sponsor in accordance with applicable federal and provincial regulations. The informed consent may be signed on paper or electronically, as approved by the IRB. The informed consent process may be conducted remotely via videoconference (Zoom, Teams, etc.). After a patient is deemed eligible from the screening process, study team members will approach the patient or schedule a videoconference to explain the study. If the consenting will be conducted remotely, the informed consent document shall be securely provided to the subject prior to the scheduled videoconference. The study staff will thoroughly explain the purpose, procedures of the study in respect to subject's involvement and responsibilities, potential risks and benefits, subject's rights and privacy of the data collected. In addition to the full disclosure of the risks and benefits of participating in the study, patients will be informed that their participation is voluntary and their decision will not impact patient care. They will be given adequate time to ask questions regarding the study and to discuss with family and friends before making the decision. At this point the subject will be asked to sign the research consent form. If consent is being obtained remotely, consents will be signed electronically using an e-signature service such as Adobe sign, DocuSign, etc. by both the subject and the person obtaining consent.

All signed consent and HIPAA forms will be kept at the site and are only accessible to study team members. If the patient refuses to participate, the patient will not be enrolled in this study. The original signed consent will be filed in a secure, locked cabinet with the subject's other original study documents. A copy of the signed consent should be filed in the hospital/clinical chart. A copy of the signed consent and HIPAA/data protection authorization must be provided to the subject. The Principal Investigator (PI) is responsible for ensuring any new information related to the study will be provided to the subject. The subject may need to be re-consented to continue participation, if required by the IRB.

The subject will be assigned a non-identifying subject number for the data collected in this study. The Investigator shall retain a copy of the signed informed consent document in each subject's record. The subject shall be provided with a copy of the signed informed consent document.

7.3 Study Procedures

Study procedures will be conducted according to the schedule outlined in Table 1 below and recorded in REDCap. See Appendices for scales, questionnaires, and assessments to be used in the study. Any adjustments to or replacements of these appendices will be justified with documentation in study files.



[redacted]

7.3.1 Preoperative

During the pre-operative period, the Investigator and/or staff delegated for this task shall verify eligibility criteria for the subject. If the subject does not meet all eligibility criteria and they have already been enrolled into the study, they will be notified and removed from the study. As part of the eligibity screening, subjects with a PROMIS Anxiety raw score of >19 will be removed from the study.

Following written consent the subject's demographic information, including but not limited to, age, weight, height, race, and ethnicity will be recorded on the CRF. In addition, a complete medical, vital signs, medication (including opioids), and surgical history, family medical history (chronic pain, addiction, cardiac, cancer, etc) EKG, PROMIS (Patient-Reported Outcomes Measurement Information System) assessments covering anxiety, depression and pain catastrophizing may be captured.

[redacted]

7.3.2 Intraoperative

The surgery will be perfomed under spinal plus sedation. Intraoperative patient management will be according to standard of care protocol.

7.3.3 Postoperative

Once the surgery is over and the patient is transferred to the recovery room, the patient will continue to receive postoperative pain control per standard of care, as determined by the anesthesia and surgical teams. Research assessments that will be collected by the research team will include [redacted]

7.3.4 Blinding and Randomization

7.3.4.1 Subjects will be randomized at point of enrollment.

[redacted]

7.3.4.4 Unblinding subject's treatment assignment to the entire study staff will only be done when necessary (i.e. for the treatment of an adverse event).

[redacted]

7.3.5 Bridge Device Placement

[redacted]

7.3.6 Bridge Device Home Instructions

[redacted]

7.3.7 Discharge

[redacted]

7.3.8 Study Follow-up

Subjects will be contacted via a phone call for follow-up visits at 1 week and 1 month. [redacted]

7.3.9 Study Completion

The subject is considered to have completed the study after they have worn the Bridge device [redacted]

8 STATISTICAL PLAN

8.1 Sample Size

This study may enroll up to 60 subjects. Descriptive statistics will be presented as mean ± SD. Continuous variable will be reported as median (95 % confident interval). Using SPSS, a one tailed unpaired t-test will be performed to assess the difference in pain between groups. Overall difference between groups over the 5 days will be assessed using an analysis of variance follow by Bonferroni test. [redacted]

8.2 Acceptance criteria

The primary outcome measured will be the total opioid consumption for the 5 day period following surgery. Secondary outcome will include pain, PONV, and functional recovery at 24, 48, 72, 96 and 120 hrs post operatively. The subject will be asked to rate the tolerance of the device using a 1-5 scale (1 being extremely poorly tolerated and 5 being extremely well tolerated) every postoperative day until day 5. Safety and Adverse Events not related to the surgery or the hip implant will be collected postoperatively every day for the first 5 days, and at 1 week and 1 month.

8.3 Definitions

The definitions for adverse event, adverse device effect, serious adverse event, serious adverse device effect, and unanticipated adverse device effect are provided below (ISO 14155:2011, 21 CFR 812.3(s)).

- Adverse Event (AE): an adverse event is any untoward medical occurrence in a subject which need not be related to the device under investigation.
- Adverse Device Effect (ADE): an adverse device effect is any untoward or unintended response to a medical device which may result from insufficiencies in the instructions for use or deployment of the device, or from use error.
- Serious Adverse Event (SAE): a serious adverse event is an adverse event that results in death, inpatient hospitalization, severe or permanent disability, a life threatening illness or injury, fetal distress, fetal death, a congenital abnormality, a birth defect, or medical or surgical intervention to prevent permanent impairment to body or structure.
- Serious Adverse Device Effect (SADE): a serious adverse device effect is an adverse device effect that results in death, inpatient hospitalization, severe or permanent disability or is life threatening.
- Unanticipated Adverse Device Effect (UADE): any serious adverse effect on health or safety or any life threatening problem or death caused by or associated with, a device, if the effect, problem, or death was not previously identified in nature, severity or degree of incidence in the investigational plan, or application (including a supplementary plan or application) or any other unanticipated serious problem associated with a device that is related to the rights, safety or welfare of subjects. Refer to the Device Risk Analysis and Risk Assessment section for details on anticipated adverse device effects.

8.4 **Anticipated Adverse Events:**

- Bleeding or infection at the puncture site
- Skin irritation
- Pain at the site of application
- Allergic contact dermatitis to the compound benzoin tincture.

8.5 **Adverse Event Reporting:**

- All Adverse Events, both Anticipated and Unanticipated, must be recorded within the CRF on the Adverse Event Report Form.
- All Adverse Events must be promptly reported to the Sponsor.
- All Unanticipated Adverse Device Effects will be also reported to both the Sponsor and the IRB.
- Both Serious Adverse Events and Unanticipated Adverse Device Effects must be reported to the Sponsor within 48 hours. All other Adverse Events should be reported to the Sponsor within 5 business days.
- All Serious Adverse Events will be also reported to the IRB per IRB reporting requirements. These reports may include, but will not be limited to: date of onset; brief description of the events; their treatment; whether they resulted in death, inpatient hospitalization, severe or permanent disability or were life threatening; their relationship to the study device; and resolution.

8.6 **Deviations from the study protocol**

Deviations from the protocol must receive both Sponsor and the investigator's IRB approval before they are initiated with the exception that under emergency circumstances, deviations from the protocol to protect the rights, safety and well-being of human subjects may proceed without prior approval of the sponsor or the IRB. Any protocol deviations initiated without Sponsor and the investigator's IRB approval that may affect the scientific soundness of the study, or affect the rights, safety, or welfare of study subjects, must be documented and reported to the Sponsor and to the investigator's IRB

as soon as a possible, but no later than 5 working days of the protocol deviation. If protocol deviations continue to occur frequently at a study site, a corrective and preventive action (CAPA) may be opened by the Sponsor.

8.7 Withdrawal of IRB approval

An investigator shall report to the sponsor a withdrawal of approval by the investigator's reviewing IRB as soon as possible, but no later than 5 working days of the IRB notification of withdrawal of approval.

9 VULNERABLE POPULATIONS

9.1 Definition

Vulnerable populations are defined as disadvantaged sub-segment of the community requiring utmost care, special considerations and protections in research. This study will recruit subjects from the following: economically disadvantaged or unemployed, educationally disadvantaged and/or Non-US citizens.

9.2 Protection of vulnerable subjects

- Educationally disadvantaged subjects will be provided ample time to ask questions and comprehend information.
- Medical care will be provided to these subjects if they are injured as a direct result of participating in this research study. The cost of treatment for any research related injury will be covered by Masimo.

9.3 Subject Compensation

Subjects will be compensated for their participation in the study.

9.4 Responsible Parties

The IRB will review research with vulnerable populations and evaluate consent, level of risk, coercion, and the reason for choosing this particular subject population. The IRB will be responsible for determining what practices will include continuing review for compliance while monitoring these studies.

The Investigator holds the ultimate responsibility for protecting the rights, safety, and welfare of research subjects by ensuring that all regulations and proper documentation of consent is handled in a compliant and timely manner.

10 DATA MANAGEMENT

10.1 Confidentiality of Records

Information about the subjects will be kept confidential. The data will be stored on a password protected database on a secure server, accessible only to the Investigators. Study data that will be released to Masimo and other regulatory authorities will be de-identified and will only pertain to study data collection, demographics, device location of the sensor, and the recordings from the pulse oximeter.

10.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, recorded data from automated instruments, and copies or transcriptions certified after verification as being accurate and complete. For this study, the case report forms may also be used as source worksheets.

10.3 Case Report Forms

An EDC system will be utilized to capture study data and compliant with 21 CFR Part 11. Data entry will be performed by site personnel after completing an appropriate training. Modifications to EDC will be made if deemed necessary by the study Sponsor.

Study data will be collected in electronic case report forms (eCRFS) but may also be collected on paper CRFs. Data will be entered into the case report form by study personnel delegated to the task by the study investigator. CRFs will be completed for all subjects, including those who do not complete study and/or are withdrawn from study. Reason for withdrawal from study will be documented. Data Collected on the CRFs will include the following information, but not limited to : inclusion/exclusion criteria, whether patient consent was obtained before start of study, demographic information, patients medical, surgical and medication histories, pre and post-surgical assessments listed in Table 1, occurrence of any adverse event, protocol deviation, and device deficiencies, etc. The CRFs will be signed by the PI to attest that the data is complete and accurate.

CRF entries will be verified by study monitor and any errors or inconsistencies will be queried to the site on an ongoing basis. Query resolution will be assessed and confirmed by study monitor during site visit. The final, completed eCRFs will be initialed/signed and dated by the PI or delegated personnel.

10.4 Record Retention

All study information, including but not limited to study correspondence, study logs, device accountability records, consent forms, subject records, and copies of CRFs should be maintained in the Investigator site files.

Study records shall be retained during the study and for a minimum of two years after date of study closure or date when records are not required to support 510(k) clearance. The Institution's own retention policies and regulations may apply in addition to the minimal requirement.

The Sponsor is responsible for verifying study data, retaining records, analyzing data, and authoring study reports.

11 MONITORING PLAN

11.1 As the Sponsor of this clinical investigation, Masimo Corporation is required by 21 CFR Part 812, of the Food and Drug Administration regulations to monitor and oversee the progress of the investigation. The monitor(s) assigned by Masimo Corporation to this task will be a direct employee from the Clinical Research department trained on departmental SOPs on conduct and monitoring of sponsored studies.

11.2 In accordance with good clinical practices guidelines, there will be at least three scheduled monitoring visits to ensure overall regulatory compliance of the study:

- An initiation visit, prior to any subject enrollment to confirm site readiness, and to document training on the study protocol and procedures, and use of equipment.
- At least one monitoring visit during enrollment when 10-15% have been enrolled, a visit when approximately 30 subjects have been enrolled, and approximately every 3 months thereafter.
- A final close out visit after the last patient had finished the study.
- NOTE DURING COVID-19 PANDEMIC: on-site monitoring visits may be unlikely. Monitoring activities may be modified or postponed until such a time that restrictions prohibiting travel and hospital access are lifted.

11.3 The monitor will contact and visit the investigator and will be allowed, on request, to have access to all source documents needed to verify the entries in the CRFs and other GCP-related documents (IRB approvals, IRB correspondences, and ICFs) provided that subject confidentiality is maintained in agreement with HIPAA regulations.

11.4 It will be the monitor's responsibility to inspect the CRFs at regular intervals throughout the study, to verify the adherence to the protocol and the completeness, consistency and accuracy of the data being entered on them.

11.5 During each visit, the monitor will also verify presence of informed consent, adherence to the inclusion/exclusion criteria, and documentation of SAEs/SADEs and protocol deviations/violations, and check CRF against source documentation.

11.6 After each visit, the monitor will provide a monitoring report to the investigator within 4 weeks of visit completion. The monitoring report will detail findings and open action items observed during the visit. It is the responsibility of the Principal Investigator and Study Coordinator(s) to respond to the findings of the monitoring report, and complete any open action items as soon as possible but no later than 60 days of receiving the monitoring report. Any open action items not completed within the time allowed may be sufficient grounds for study site suspension or termination; it will be up to the sponsor to determine whether any incomplete action items are sufficient grounds for suspension or termination. See Section 13 for details on suspension and termination.

11.7 Depending on the quality of the data and/or changes to factors affecting patient safety, additional monitoring visits may be necessary according at the sponsor's discretion.

11.8 The Investigator will provide the monitor access to all necessary records to ensure the integrity of the data (21 CRF 812).

12 ADMINISTRATIVE ASPECTS

12.1 Protection of Human Subjects

Per 21 CFR 50, written consent must be obtained from each subject prior to any study procedures in accordance with applicable federal, state, and study site regulations. The Investigator must keep a copy of the signed consent form in each subject's record and provide a copy to the subject as well. The Investigator shall not allow a subject to participate in a study or sign consent prior to IRB approval.

Prior to the start of data collection or subject enrollment, the Investigator must provide documentation of IRB approval of the study protocol and a copy of the approved informed consent form (21 CFR 50).

All subjects will be monitored closely throughout the study. The following measures will be taken to ensure the privacy of subjects:

- A code (unique identification) number for each subject will be kept on file.
- Only their correspondence identification number will identify subjects.
- Access to the documents and data will only be made to the Investigators and study staff in the study.
- The confidentiality of these documents will be protected to the extent provided by the law.

12.2 Institutional Review Boards

The Sponsor and/or Investigator must submit the protocol to the appropriate IRB and obtain a copy of the written and dated approval letter.

The approval letter should state the name of the documents reviewed, date of review, date of approval, and reference the study name (protocol title, study number, and version).

The informed consent used by the Investigator must be reviewed and approved by the Sponsor prior to submission to the IRB. The Investigator cannot enroll subjects until a copy of the approved informed consent is obtained from the IRB.

Any amendments to the protocol or informed consent should be submitted to the IRB for review and approval per 21 CFR 56. The IRB should be notified of any changes that may affect conduct of the study or pose safety risks to the subjects.

12.3 Confidentiality

All data collected will be kept confidential and de-identified. It can only be accessed by researchers and will be used for research purposes only.

12.4 Protocol Amendments

Any changes made to the clinical investigational plan/study protocol will be documented by way of an amendment. Before submitting protocol amendment to the IRB for approval, the protocol amendment must be agreed upon and signed by both the Investigator and the Sponsor. The Investigator shall not make any changes to the protocol without Sponsor approval and documented approval from the IRB. Both PI and Sponsor will retain the IRB approval letter and approved protocol as confirmation that the protocol amendment was approved.

12.5 Suspension or Termination of Study Site

The Sponsor can suspend or prematurely terminate the PI's and study site's participation in the study, particularly if Sponsor finds serious non-compliance by the PI or site, and if such non-compliance was not resolved in a timely manner. The Sponsor will document the decision to suspend or terminate the investigation in writing. A suspended study site cannot enroll new subjects.

If the Sponsor determine that the study site's compliance to GCP and federal regulations to be inadequate at any point during the study, and Sponsor move to suspend or terminate the study site, the Sponsor will provide notification in writing to the principal investigator and IRB as necessary. The study site is eligible for reinstatement upon correction of any findings and any open action items prior to the suspension, and provides a written guarantee that the same non-compliance will not reoccur in the future. Site can only resume patient enrollment upon receiving written notification of reinstatement from the Sponsor and/or IRB.

12.6 Termination of Clinical Investigation/Study due to UADE

The clinical investigation may be terminated if Sponsor determines that an unanticipated adverse device effect presents an unreasonable risk to the subjects. Termination shall occur not later than 5 working days after the Sponsor makes this determination, and not later than 15 working days after the Sponsor first received notice of the effect.

The Sponsor may resume the terminated clinical investigation with prior IRB approval if the device is non-significant risk.

13 AGREEMENT BETWEEN INVESTIGATOR AND SPONSOR REGARDING RESPONSIBILITIES FOR GOOD CLINICAL PRACTICE

International Conference of Harmonization (ICH) E6 Good Clinical Practice guidance is an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects.

It specifies general requirements intended to:

- Protect the rights, safety and well-being of human subjects,
- Ensure the scientific conduct of the clinical investigation and the credibility of the clinical investigation results,
- Assist sponsors, monitors, investigators, ethics committees, regulatory authorities and other bodies involved in the conformity assessment of medical devices.

The Principal Investigator of the clinical investigation shall:

- Obtain and maintain IRB approval of the study.
- Ensure all subjects are consented prior to enrollment, per FDA Code of Federal Regulations titled 21 CFR 50.
- Ensure only appropriately trained personnel will be involved in clinical investigation.
- Maintain study records mentioned in the CIP.
- Maintain logs for study team delegation, site visit/monitoring, equipment disposition, study team training, subject recruitment and enrollment.
- Evaluate all adverse events and adverse device effects and determining whether the study is safe to continue.
- Allow the sponsor to conduct periodic monitoring of study activities to ensure GCP compliance.
- Not promote device prior to clearance by FDA for commercial distribution, except for academic purposes and scientific presentations.

The Sponsor shall insure existence and record of all necessary compliance documents, and will conduct monitoring visits to ensure appropriate conduct of the study

14 REVISION HISTORY

15 REFERENCES

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16 APPENDICES