**Official Title:** Pulsed Electromagnetic Fields for Postoperative and Post-Amputation Analgesia: A Randomized, Participant- and Observer-Masked, Sham-Controlled Pilot Study

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**UCSD Human Research Protections Program**

# New Biomedical Application
# RESEARCH PLAN

Instructions for completing the Research Plan are available on the HRPP website.
The headings on this set of instructions correspond to the headings of the Research Plan.
General Instructions: Enter a response for all topic headings.
Enter "Not Applicable" rather than leaving an item blank if the item does not apply to this project.

Version date: 9/30/2013

## 1. PROJECT TITLE

**Pulsed Electromagnetic Fields for Postoperative and Post-Amputation Analgesia: A Randomized, Participant- and Observer-Masked, Sham-Controlled Pilot Study**

## 2. PRINCIPAL INVESTIGATOR

Brian Ilfeld, MD, MS

## 3. FACILITIES

UCSD health system: Thornton Hospital, Jacobs Medical Center, Hillcrest Medical Center, KOP
Amputees will self-administer the intervention in their homes in any of the 50 States of the U.S.

## 4. ESTIMATED DURATION OF THE STUDY

Three years (1 month preparation, 24 months enrollment, 11 months publication prior to closure)

## 5. LAY LANGUAGE SUMMARY OR SYNOPSIS (no more than one paragraph)

The moderate-to-severe pain many patients experience following surgery is often treated with opioids, which are associated with side effects such as nausea/vomiting, sedation, and respiratory depression (and a risk of abuse, dependence, and diversion). Potent site-specific analgesia with fewer side effects may be provided with peripheral nerve blocks. However, these too have limitations such as a duration of action measured in hours, while the pain from surgery is usually measured in days or weeks. Pulsed electromagnetic field therapy is an alternative method of pain control involving the application of electromagnetic energy. FDA-cleared devices have been in clinical use for over 70 years, demonstrating an extraordinary safety profile: these are noninvasive and non-pharmacologic devices, with no side effects, adverse events, or medication interactions; and the only contraindications are pregnancy and an implanted pulse generator such as a cardiac pacemaker. The device has no potential for dependence, abuse, or diversion. Until relatively recently, available devices consisted of a large signal generator and bulky coil applicator that were not portable and produced significant electromagnetic interference, making them impractical for common use. However, small, lightweight, relatively inexpensive, noninvasive, FDA-cleared devices that function for 30 days are now available to treat acute and chronic pain, decrease inflammation and edema, and hasten wound healing and bone regeneration. Therefore, it has the potential to concurrently improve analgesia and decrease or even negate opioid requirements following surgery, only without the limitations of opioids and peripheral nerve blocks. The purpose of this pilot study is to explore the possibility of treating acute postoperative and chronic post-amputation pain with pulsed electromagnetic field therapy, optimize the study protocol, and estimate the treatment effect in preparation for developing subsequent definitive clinical trials.

## 6. SPECIFIC AIMS

The proposed study will be a randomized, participant- and observer-masked, sham-controlled, parallel-arm, human participants pilot study with two primary aims:

***Specific Aim 1:*** To determine the **feasibility** and **optimize** the protocol for subsequent clinical trials that will compare the addition of pulsed electromagnetic field therapy to usual and customary

analgesia following moderate-to-severely painful surgical procedures or post-amputation phantom and residual limb pain.

***Specific Aim 2:*** To ***estimate*** the **treatment effect** of adding pulsed electromagnetic field therapy to usual and customary analgesia on pain and opioid consumption following moderate-to-severely painful surgical procedures or post-amputation phantom and residual limb pain. This will provide an idea of the optimal surgical procedures and amputee characteristics amenable to this analgesic technique and allow determination of the required **sample sizes** of subsequent definitive clinical trials.

***Hypothesis 1:*** *Pulsed electromagnetic field therapy decreases **pain** in the 7 days following moderate-to-severely painful surgical procedures or 28 days following application for post-amputation pain.*

***Hypothesis 2:*** *Pulsed electromagnetic field therapy decreases **opioid use** in the 7 days following moderate-to-severely painful surgical procedures.*

## 7. BACKGROUND AND SIGNIFICANCE

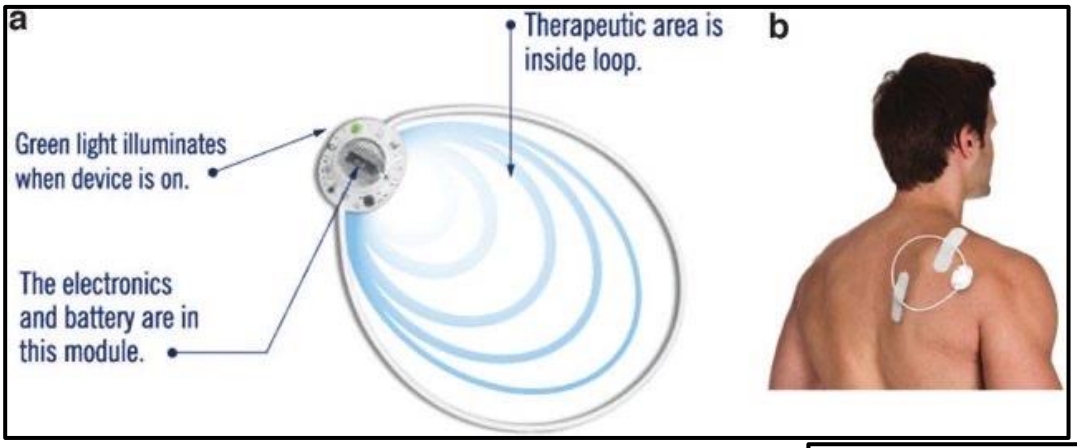
The moderate-to-severe pain many patients experience following surgery is often treated with opioids, which are associated with side effects such as nausea/vomiting, sedation, and respiratory depression (and a risk of abuse, dependence, and diversion). Potent site-specific analgesia with fewer side effects may be provided with peripheral nerve blocks. However, these too have limitations such as requiring an anesthesiologist for administration, a duration of action measured in hours, and rendering the target area/limb insensate.

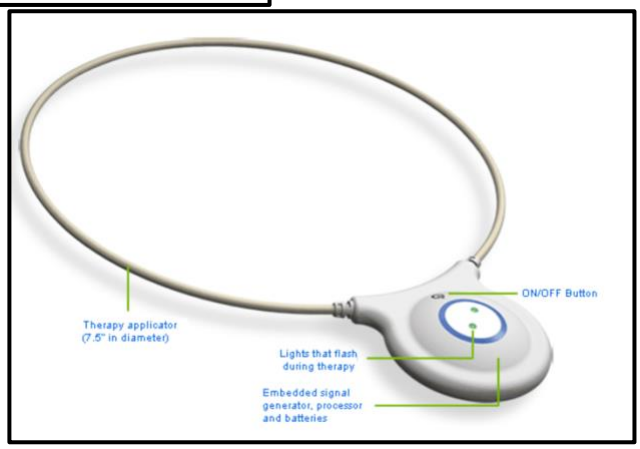
An analgesic alternative with few associated limitations is **pulsed electromagnetic field (PEMF)** therapy, also called pulsed short-wave therapy, pulsed radiofrequency energy therapy, and radiofrequency nonthermal diathermy.[1] Over the last 7 decades, PEMF has been used to treat acute and chronic pain, decrease inflammation and edema, and hasten wound healing and bone regeneration.[1] Possible mechanisms for the multiple clinical effects of PEMF are multifactorial, complex, and only partially understood.[1] The primary theory involves the promotion of calcium binding to calmodulin which activates endothelial and neuronal nitric oxide synthase isoforms, producing nitric oxide which has anti-inflammatory and analgesic effects, among other consequences such as decreasing edema while increasing blood and lymph flow.[1]


In 1947, the United States Federal Communications Commission assigned three frequencies for radiofrequency use in medical treatments: 40.68, 13.56 and 27.12 MHz.[1] Within just a few years, the first pulsed electromagnetic field generator was cleared by the United States Food and Drug Administration for use with patients using 27.12 MHz: the Diapulse.[2,3]. Until relatively recently, available devices consisted of a large signal generator and bulky coil applicator that were not portable and produced significant electromagnetic interference, making them impractical for common use (**Figure, right**). However, over the past 70 years they have exhibited an extraordinary safety profile: these are noninvasive, nonpharmacologic devices, with no side effects, adverse events, or medication interactions; and the only

contraindications are pregnancy and an implanted pulse generator such as a cardiac pacemaker. Unlike opioids, there is no risk of abuse, dependence, and/or diversion.

More recently, small, simple, lightweight, battery-powered, noninvasive PEMF devices have received FDA clearance for use treating acute and chronic pain, including the ActiPatch and RecoveryRx for amputees and the initial 150 surgical subjects of Phase I (Model 088, BioElectronics, Frederick, Maryland; **Figure, below left**); as well as SofPulse for the subsequent 80 surgical subjects of Phase II (Endonovo Therapeutics, Woodland Hills, California; **Figure below right**). We will be using the devices for FDA-approved indications; in other words, on-label use.




First described as a therapy to treat postoperative pain in the 1960s,[4] multiple investigations suggest analgesic benefits following various types of surgical procedures, including breast reduction,[5] reconstruction,[6] and augmentation;[1,7] anterior cruciate ligament reconstruction;[8] molar extraction;[9] and cesarean section.[10] Chronic pain conditions have also been treated with PEMF therapy, including knee osteoarthritis and failed back surgery syndrome.[11,12] However, PEMF has not found widespread use, probably due to the cost and size of the initial large console devices; and later lacking credibility due to scant randomized data. What studies have been published generally involve small sample sizes,[1,5,7] lack a control group,[13] lack prospective registration,[10] and/or authors with a significant conflict-of-interest.[1,8,14-19]

Nevertheless, there appears to be extraordinary unrealized potential for PEMF to treat acute and chronic pain: it can be easily applied in less than one minute by a layperson using tape, induces no side effects (it induces no perceptible sensations at all), is completely noninvasive, is lighter and

thinner than many surgical bandages, may be applied to nearly any part of the body, functions through clothing or bandages, has only two contraindications (pregnancy and an implanted pulse generator), requires no intervention by patient or provider, has a duration of up to 30 days (unlimited duration using serial devices), has not resulted in any adverse events, has no abuse/dependence/diversion potential, and is relatively inexpensive compared to most other analgesics. ***Due to its demonstrated benign profile and relatively low cost, PEMF could be applicable to nearly <u>every</u> painful surgical procedure and chronic pain condition***, similar to acetaminophen and NSAIDs (only without every 6-hour patient/provider administration and the potential toxicity of acetaminophen and side effects/complications of NSAIDs).

Consequently, we propose a randomized, participant- and observer-masked, sham-controlled, parallel-arm clinical pilot study to demonstrate feasibility and optimize the protocol as well as estimate the treatment effect to help design and power subsequent definitive, multicenter, randomized, controlled clinical trials. ***The primary hypotheses are that PEMF decreases pain (and opioids for surgical patients) in the 7 days following moderate-to-severely painful surgical procedures or 28 days following application for post-amputation pain.***

## 8. PROGRESS REPORT

N/A

## 9. RESEARCH DESIGN AND METHODS

This will be a single-center (UCSD), randomized, participant- and observer-masked, sham-controlled, parallel-arm human subjects pilot study.

**Enrollment.** Participants will be consenting adults either (1) undergoing various surgical procedures usually resulting in moderate-to-severe postoperative pain, or (2) experience post-amputation phantom and/or residual limb pain. Study inclusion will be proposed (1) to eligible presurgical patients or (2) after an amputee contacts the investigators. If an individual desires study participation, written, informed consent will be obtained using a current UCSD IRB-approved ICF. The study population of interest includes adult women and men of all races, ethnicity, sexual identity, and socioeconomic status. Inclusion and exclusion criteria are listed in section #10 below.

**Procedures.** Following written, informed consent, we will record baseline anthropometric information (age, sex, height, weight, amputation details and current pain levels). Surgical participants will receive any standard peripheral nerve block(s) administered using bupivacaine or ropivacaine 0.5% with epinephrine (standard at UCSD) prior to undergoing their surgical procedure *per standard of care*.

**Treatment Group Assignment.** Each participant will be randomized to one of two treatment groups: ***Active*** or ***Sham*** treatment. For the initial 150 subjects of Phase I, there are sham RecoveryRx devices produced that are identical to active RecoveryRx devices, only they do not deliver PEMF. Randomization will be stratified by surgical procedure/amputation, in block sizes of 2. The computer-generated randomization lists will be created by the University of California San Diego Investigational Drug Service in a 1:1 treatment group ratio using opaque envelopes. For the initial 150 subjects of Phase I using RecoveryRx devices, the active and sham devices are indistinguishable in appearance, and therefore investigators, participants, and all clinical staff other than the individual who opens the randomization envelope and chooses a sham or active device will be masked to treatment group assignment for the duration of the data collection period. For the subsequent 80

subjects of Phase II, active SofPulse devices will be provided to patients randomized to the active treatment group; and sham RecoveryRx devices will be provided to the patients randomized to the sham treatment group.

**Study intervention.** For surgical patients of Phase I, the PEMF device (2 devices, if there are multiple incisions or the incision is larger than the device diameter; 3 devices for total knee and hip arthroplasty or spinal surgery) will be affixed over the primary wound area(s) using tape and activated prior to recovery room discharge *(Experimental)*. For surgical patients of Phase II, a single PEMF device will be used for each participant due to their larger diameter and treatment area. For amputees, the device used is over-the-counter (ActiPatch, BioElectronics, Frederick, Maryland) and 2 devices (both the same treatment group) will be shipped to the patient either in or out of California who will then contact an investigator for assistance in self-placement of the device on the residual limb. The optimal location to treat phantom pain is currently unknown and will partially informed by the results of this pilot study, and patients will be encouraged to move the devices to a new anatomic location every two days until relief is experienced.

**Supplemental analgesics.** In addition to the PEMF device(s), participants will receive standard-of-care supplemental analgesics which can include acetaminophen, ibuprofen, ketorolac, opioids, gabapentin (this is provider- and patient-dependent). *Therefore, <u>all</u> patients of this study—regardless of the treatment arm they are randomized to—will continue to receive current usual and customary analgesia: all will receive the same combination of supplemental analgesics they would regardless of study participation (of note, amputees will be asked to continue their normal analgesic regimen, including any as-needed treatments).* Participants (and their caretakers of surgical patients) will be provided with verbal and written instructions, and the telephone and pager numbers of an investigator available during business hours throughout the treatment period. Participants can shower with the device in place, but not submerge it during swimming or a bath, as advised by the manufacturer.

Surgical participants will be discharged with their PEMF device(s) *in situ* and a prescription for immediate-release oral opioid, preferably oxycodone 5 mg tablets, taken for breakthrough pain (surgeons occasionally prefer a different type of opioids such as hydrocodone, which is why we analyze the data using oral oxycodone equivalents). The PEMF devices will be removed by participants at home following Day 8 (SofPulse) or Day 30 (Actipatch/RecoveryRx) when the battery is exhausted (participants may remove them as early as Day 7, if they desire). Removing the devices encompasses tape removal and discarding in the trash (these are disposable, single-use devices).

Amputees will return their initial devices in pre-addressed and -stamped envelopes that we provide. They will be sent a second device which is the opposite treatment of the initial device: participants who initially received sham will subsequently receive active, and vice versa. These will be applied on Day 35 and the same protocol will be repeated as for the initial device, with additional data collected for 35 days after placement of the second device. The second device will be discarded in the trash.

Of note, if a device is reported lost or nonfunctional during the study, it will be replaced by the investigators by mail if more than 7 days of treatment remain.

**Outcome measurements (end points).** We have selected outcome measures that have established reliability and validity, with minimal inter-rater discordance, and are recommended for pain-related clinical trials by the Initiative on Methods, Measurement, and Pain Assessment in

Clinical Trials (IMMPACT) consensus statement. All data collection will be through standard UCSD EPIC notes and patient interviews in-person during hospitalization or *via* a telephone call for outpatients. Postoperatively, surgical endpoints will be recorded such as surgical duration. All pain scores will be measured using the Numeric Rating Scale (0: no pain, 10: worst imaginable pain). On Days 35 and 70, amputees will be asked if they would want to continue using the device; and on Day 28 surgical patients will be asked if they would want to use the device if they were to have the same surgery in the future? For Phase II surgical participants, Days 21 and 28 will be excluded due to the shorter treatment period (8 days) of this device relative to that used in Phase I. At all time points for amputees, phantom and residual limb pain will be distinguished and recorded separately.

**Summary of post-enrollment assessments** (color added for clarity)

| **Time Point:** | ***Surgical Patients*** Postoperative Days | | | | | | | | ***Amputees*** Post-Application Days | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 7 | 14 | 21 | 28 | 180 | 0 | 2 | 4 | 7 | 21 | 28 | 35 |
| **Opioid** consumption | • | • | • | • | • | • | • | • | • | • | • | • | • | • | • |
| **Average Pain** [NRS] | • | • | • | • | • | • | • | • | • | • | • | • | • | • | • |
| **Worst Pain** [NRS] | • | • | • | • | • | • | • | • | • | • | • | • | • | • | • |
| **Brief Pain Inventory**, Short Form | | | | • | • | • | • | | • | | | | | • | • |
| **Patient Global Impression Change** | | | | | | | | | | • | • | • | • | • | • |
| **Sleep disturbances (#)** previous night | • | • | • | • | • | • | • | | • | • | • | • | • | • | • |
| **Passive flexion** (knees and hips) | | | | | • | | | | | | | | | | |

**Primary end points:** This is an exploratory pilot study to assist in planning subsequent definitive trials and we therefore have no data analysis plan. For surgical patients, the two outcomes of primary interest will be (1) the "average" and "worst" pain measured with the Numeric Rating Scale (included in the Brief Pain Inventory pain domain), and (2) opioid consumption within the first 7 postoperative days. For amputees, the outcome measures of primary interest will be (1) the change in "average" residual and phantom limb pain scores between baseline and Day 28 of the initial treatment, as well as (2) the Patient Global Impression of Change on Day 28 of the initial treatment.

For Phase II, there will be a total of 70 surgical participants, and these patients will be analyzed separately from Phase I surgical and amputation patients. Sample size calculations are based upon the hypothesis that pulsed electromagnetic field therapy decreases **pain** in the 7 days following moderate-to-severely painful surgical procedures. The primary outcome calculated as follows: for each participant all of the "average" and "worst" daily pain scores collected within the first 7 postoperative days will be summed. We will use these summed scores from participants having cholecystectomy (n=30), and hip and knee arthroplasty (n=40) to estimate a probable sample size.

We will consider a 33% reduction in pain scores to be the minimal clinically important difference [Farrar et al. J Pain Symptom Management 2003; 25: 406-11]. Based on values from patients receiving sham in Phase I, we anticipate the sham group to have an anticipated mean (SD) of 23.9 (12.3). Assuming a two-sided type I error protection of 0.05 and a power of 0.80, approximately 25 patients in each group are required (ClinCalc.com, accessed 2/23/23). To allow for a higher degree of variability than anticipated we will enroll a total of 70 participants in Phase II: cholecystectomy (n=30), and hip and knee arthroplasty (n=40).

Continuous, normally-distributed data will be reported as mean ± standard deviation. Nonparametric continuous or categorical data will be reported as median [10th-90th percentiles] or precents, as appropriate. Comparisons of independent samples will be performed using Student's t-test for parametric continuous variables or Mann-Whitney U test for nonparametric or categorical variables. The Chi Square test and Fisher's Exact test will be used for differences in proportions, as appropriate. $P<0.05$ will be considered statistically significant for the primary outcome. Results of comparisons in secondary outcomes will be interpreted as suggestive, requiring confirmation in a future trial before considering them as definitive.

## 10. HUMAN PARTICIPANTS

We will recruit a convenience sample with a maximum of **270 participants in total (all participants who sign an informed consent included)**. Selection for inclusion will not be based on race, ethnicity, sexual identity, or socioeconomic status. There will be no participants from vulnerable populations, such as pregnant women, children, or prisoners.

***Inclusion criteria (amputees):*** Adult patients of at least 18 years of age [19 years in Alabama and Nebraska], (1) with an upper or lower limb amputation at least 12 weeks prior to enrollment distal to the shoulder or hip (femoral head remaining), respectively, and including at least one metacarpal or metatarsal bone, respectively; (2) who experience at least moderate residual and/or phantom limb pain—defined as a 3 or higher on the Numeric Rating Scale (NRS; 0-10, 0= no pain; 10=worst imaginable pain)—at least daily for the previous 2 months; and (3) willing to avoid both changes to their analgesic regimen as well as elective surgical procedures for 70 days after initiation of treatment with PEMF therapy.

***Inclusion criteria (surgical patients):*** Adult patients of at least 18 years of age undergoing one of the surgical procedures listed below:

a. non-mastectomy breast surgery with a single-injection paravertebral nerve block
b. laparoscopic or open cholecystectomy
c. laparoscopic sleeve gastrectomy
d. percutaneous nephrolithotomy
e. ventral hernia repair
f. inguinal hernia repair
g. knee or hip arthroplasty
h. foot/ankle surgery with at least moderate pain anticipated
i. shoulder acromioclavicular joint repair, labral repair, subacromial decompression, or Bankart repair (without rotator cuff repair)
j. hand/forearm/elbow/shoulder surgery with at least moderate pain anticipated
k. spinal surgery with at least moderate pain anticipated

***Exclusion criteria:*** (1) concurrent use of an implanted pulse generator (e.g., cardiac pacemaker); (2) pregnancy; (3) incarceration. **Surgical participants only:** (4) chronic opioid/tramadol use (daily use within the 2 weeks prior to surgery and duration of use > 4 weeks); (5) neuro-muscular deficit of the surgical area/limb; (6) a planned postoperative perineural local anesthetic infusion.

**11. RECRUITMENT AND PROCEDURES PREPARATORY TO RESEARCH**

**Amputees.** The Primary Investigator will place Institutional Review Board-approved study advertisements within print and web-based publications that are frequently read by the target population. Additionally, site directors will provide similar Institutional Review Board-approved advertising material to the leaders of local and regional amputee focus/support groups. Individuals who are interested in the study will be directed to contact the study investigators or research coordinators for a thorough description of the study purpose and protocol. Finally, chronic pain physicians will be provided with the IRB-approved advertisements to give to their patients with an amputation and chronic pain.

Individuals interested in the study will contact a research coordinator or investigator by email or telephone (contact information provided in the IRB-approved advertisements). Patients meeting inclusion and exclusion criteria will be presented with the study and provided the IRB-approved ICF and HIPAA consent electronically for their review. Individuals wishing to participate will have the option to (1) print the IRB-approved consent forms, sign the forms, and return them via the postal service; or (2) have UCSD send them the consent forms via a postal service, of which they may then sign and return in pre-addressed and stamped envelopes provided in the original envelope. Following receipt of the signed consent forms, participants will be randomized and sent an active or sham PEMF device by a postal service with instructions to contact the investigative team upon arrival for assistance in applying the device.

**Surgical participants.** The investigators will need to know in advance which patients would like to participate in order to have a research coordinator present on the day of surgery. The investigators therefore need to contact potential participants prior to their pre-surgery visit and ***request a partial waiver of HIPAA authorization for recruitment purposes***. We will scan the upcoming surgery schedule (which we have access to being anesthesiologists—we use this schedule daily for medical purposes), identify patients having the types of surgical procedures specified for this study, look in their electronic records to determine eligibility, and if eligible either call the potential participants ourselves or provide the name and contact information to a research coordinator to contact the potential participants.

1. These procedures are minimal risk to the potential participants as we are anesthesiologists who will be viewing these records even without study participation in preparation for surgery and postoperative analgesia planning. There is no information that an anesthesiologist would not view regardless of the existence of the study.

2. A partial waiver of HIPAA authorization for recruitment purposes would not adversely affect the rights and welfare of the potential participants as we are anesthesiologists who will be viewing these records even without study participation in preparation for surgery and postoperative analgesia

planning. There is no information that an anesthesiologist would not view regardless of the existence of the study.

3. This clinical trial could not be practicably carried out without the partial waiver because many relatively healthy ambulatory patients are not seen in preop clinic; or they are seen just 1-2 days prior to their date of surgery. The investigators will need to know in advance which patients would like to participate in order to have a research coordinator present on the day of surgery.

4. After participants are contacted, if they would like to participate, they will receive written, informed consent using an IRB-approved informed consent form.

These procedures would also include access to PHI:

1. Identifiers will include the potential participant's date of surgery, surgeon, name, phone number, and email address (to send ICF if patient is interested in participation). This information will be recorded in hard-copy format and destroyed using a paper shredder (or in the locked UCSD PHI disposal stations) following contact with the patient. If the patient does not participate, then there will be no record of PHI whatsoever. If the patient does participate, then PHI will be protected as described in #16 below.

2. This clinical trial could not be practicably carried out without the partial waiver because many relatively healthy ambulatory patients are not seen in preop clinic; or they are seen just 1-2 days prior to their date of surgery. We need to schedule a research coordinator to be present for the day of surgery.

3. The privacy risk to individuals whose PHI will be used is minimal since, as anesthesiologists at UCSD caring for ambulatory surgery patients, we use the surgery schedule daily in the normal course of our work caring for patients; and we will not record any PHI other than date of surgery, surgeon, name, contact phone numbers, and email address—and these will be destroyed following use. The anticipated benefit to participants is a chance of improving their postoperative pain control if they are randomized to active stimulation.

4. PHI that will be used includes date of surgery, surgeon, name, contact phone numbers, email address, basic anthropometric data such as height and weight, past medical and surgical history, and the surgical schedule itself. Only coinvestigators will access this PHI, and the only people they might share it with are research coordinators actively participating in this research who understand PHI procedures and to appropriately destroy the hard copy of date/surgeon/name/contact numbers/email address after use.

Patients meeting inclusion and exclusion criteria will be presented with the study, and prospective study participants desiring additional information will be required to give permission for a research coordinator to contact them to adhere to HIPAA requirements. The study protocol will be reviewed with interested prospective participants in detail; and for participants desiring participation, written, informed consent will be obtained prior to any measurements, data collection, and/or interventions. The method of documenting consent will be using written informed consent forms approved by the local Institutional Review Board.

**12. INFORMED CONSENT**

**Amputees.** Individuals interested in the study will contact a research coordinator or investigator by email or telephone (contact information provided in the IRB-approved advertisements). Patients meeting inclusion and exclusion criteria will be presented with the study and provided the IRB-approved ICF and HIPAA consent electronically for their review. Individuals wishing to participate will have the option to (1) print the IRB-approved consent forms, sign the forms, and return them via the U.S. Postal Service; or (2) have UCSD send them the consent forms via the U.S. Postal Service, of which they may then sign and return in pre-addressed and stamped envelopes provided in the original envelope. Following receipt of the signed consent forms, participants will be randomized and sent an active or sham PEMF device by U.S. Postal Service with instructions to contact the investigative team upon arrival for assistance in applying the device.

**Surgical participants.** Candidates who meet inclusion and exclusion criteria and desire study enrollment will be scheduled to arrive the day of surgery 15 minutes earlier than normal to allow for written informed consent and baseline information collection. Written informed consent will be attained prior to any measurements or procedures prior to surgery. When participants present for surgery, research coordinators will provide and attain written informed consent. This will occur in private patient care areas, so that participants may feel comfortable asking questions of the research coordinator.

We do not foresee any issues relevant to the mental capacity of the potential human participants. Written, informed consent will be attained prior to any study procedures or measurements; and participants will not receive procedure-related sedation until following the written, informed consent process is completed. Participants will be provided privacy and time for decision making both in the study description/explanation telephone call to an investigator or research coordinator, as described above; and, the morning of the initial treatment using a private patient care area to again review the study, informed consent form, and answer any remaining questions. As noted previously, participants may speak with an investigator by telephone from initial contact through the morning of treatment; and will have access during and following the treatment(s) with cellular phone and pager numbers provided upon discharge.

This study protocol has follow-up data-collection telephone calls a maximum of 6 months following the initial study treatment (70 days for amputees), so repeated informed consent following the initial consent is unnecessary, as opposed to multi-year, longer-term clinical trials. Surrogate consent will not be accepted; therefore, if human participants cannot provide consent on their own, they will not be offered study enrollment. Consent by an individual's Legally Authorized Representative is unacceptable for study enrollment.

Following informed consent and the signing of the UCSD IRB-approved ICF and HIPAA documents, these documents will be copied, and the copy placed in the patient's medical record. The participant will be provided a copy along with the Participants' Bill of Rights.

## 13. ALTERNATIVES TO STUDY PARTICIPATION

Patients can decline enrollment. For amputees, their current analgesic regimen will not deviate due to inquiry regarding the study. For surgical patients, they will still receive the standard-of-care postoperative analgesia.

## 14. POTENTIAL RISKS

There are currently no known medical risks from PEMF, although there is the risk of an allergic reaction to the tape used to hold the device to the skin. There is the risk of loss of confidentiality. The following study procedures will be done to maintain confidentiality of this study: hard copies will be kept in locked medical offices and the locked Investigational Drug Service's files. Any digitized records containing personal health information will be stored as password-protected and encrypted files.

**15. RISK MANAGEMENT PROCEDURES AND ADEQUACY OF RESOURCES**

There are only two medical contraindications to PEMF: pregnancy and use within 6" of an implantable pulse generator. There is no known theoretical risk to a developing fetus; but since this has not been studied, pregnancy is avoided out of an abundance of caution. Modern implanted pulse generators such as cardiac pacemakers are shielded from PEMF, so keeping the PEMF device at least 6" from a pacemaker is also out of an abundance of caution as even a PEMF device placed directly over a pacemaker should have no effect on the pacemaker function. All patients undergoing surgery will have a pregnancy test as part of their regular care, regardless of study participation. Amputees will be placing the devices on their limb, and the only portion of the body that receives radiofrequency energy is within the ring of the device which will not be applied to the pelvis or lower abdomen in these patients. Regarding implantable pulse generators, there is theoretically no risk in using PEMF therapy as modern generators are shielded from such energy. However, out of an abundance of caution, we will not include any patients with an implanted pulse generator.

**16. PRIVACY AND CONFIDENTIALITY CONSIDERATIONS INCLUDING DATA ACCESS AND MANAGEMENT**

The following study procedures will be done to maintain confidentiality of this study: hard copies will be kept in a locked medical office. Only the investigators will have access to the records. Any electronic records with patient identifiers will be password protected according to UCSD IT recommendations and policies. No patient identifiers will be used in reporting data from the study. Every effort will be made to assure protection of patient privacy. The data will not be shared with the manufacturer.

This study will require access to the medical record of patients who have consented to participate as participants. The privacy of these patients will be protected in the manner described below:

1. Specific consent will be obtained from each patient to permit examination of his or her medical record.
2. Information obtained during the study will be de-identified with study specific identifiers that do not permit recognition of any participants' personal information.
3. All information gathered will be stored in a locked cabinet which is inside a locked room which will be accessible only to registered study investigators.
4. Any data gathered stored on portable electronic media (e.g. flash drives) will be stored in this cabinet when not in use.
5. Any digitized records will be stored in encrypted files on password-protected computers.
6. No photographs will be taken.

**17. POTENTIAL BENEFITS**

**For participants randomized to receive sham:** There will be no difference between being in this study and "standard" care. However, for amputees who receive a sham device initially, they will subsequently receive an active device and therefore this will not apply.

**For participants randomized to receive active stimulation:** It is our hope that patients have decreased pain, opioid consumption, sleep disturbances, and pain-induced physical and emotional dysfunction.

**Possible benefits to others:** Future patients may benefit if it is determined that PEMF therapy decreases postamputation and postoperative pain, as well as opioid requirements. Finding an effective non-opioid analgesic would be a tremendous step forward in helping future patients.

**18. RISK/BENEFIT RATIO**

There are no known medical risks of PEMF therapy, although there is the risk of allergic reaction from the tape used to secure the device to the skin. With its ease of application, lack of side effects, prolonged duration of action, and simple removal, PEMF therapy has the very real possibility of replacing opioid analgesics—the standard of care for the past 100 years—that would completely revolutionize postoperative analgesia, as we know it.

**19. EXPENSE TO PARTICIPANT**

None

**20. COMPENSATION FOR PARTICIPATION**

None

**21. PRIVILEGES/CERTIFICATIONS/LICENSES AND RESEARCH TEAM RESPONSIBILITIES**

Principal Investigator and Co-investigators are board-certified anesthesiologists with fellowship training in regional anesthesia and acute pain who place peripheral nerve blocks and manage acute pain on a regular basis. All hold a license to practice medicine in California, have medical privileges at the UC Medical Centers, and will be responsible for the overall management of this study.

Investigators: Brian Ilfeld, MD, MS; John Finneran, MD; and Engy Said, MD.

Baharin Abdullah is the current Program Manager of the Division of Regional Anesthesia and Acute Pain Medicine, and will therefore be performing regulatory work, consenting participants, mailing potential and enrolled participants, interacting with participants, and collecting data.

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**23. FUNDING SUPPORT FOR THIS STUDY**

Departmental funding and PEMF devices donated by the manufacturer: BioElectronics Corp (Frederick, Maryland).

**24. BIOLOGICAL MATERIALS TRANSFER AGREEMENT**

Not applicable

**25. INVESTIGATIONAL DRUG FACT SHEET AND IND/IDE HOLDER**

Not applicable

**26. IMPACT ON STAFF**

There will be no appreciable impact on nursing staff as the study intervention will take fewer than 5 minutes while the patient is in the recovery room and will not add to recovery room stay duration; and will not require any attention from the recovery room nursing staff.

**27. CONFLICT OF INTEREST**

None

**28. SUPPLEMENTAL INSTRUCTIONS FOR CANCER-RELATED STUDIES**

Not applicable

**29. OTHER APPROVALS/REGULATED MATERIALS**

Not applicable

**30. PROCEDURES FOR SURROGATE CONSENT AND/OR DECISIONAL CAPACITY ASSESSMENT**

Not applicable: surrogate consent will not be accepted.