ClinicalTrials.gov NCT04491175

SPIRIT Table: eProtocol M-Stim for LBP Opioid & Pain Reduction

Administrative	Description
Title	Multimodal Mechanical Stimulation to Reduce Opioids for Low Back Pain: A Randomized Clinical Trial An Outpatient, Double-blinded Randomized Trial Comparing the Impact of DuoTherm™ Mechanical Stimulation (M-Stim) Versus TENS on Opioid Prescribing and Use for Low Back Pain
Trial Registration	ClinicalTrials.gov NCT04491175
Protocol Version	NIH funded protocol submitted 5/29/2019 to FDA Q191165 IRB Protocol Submission Date: 8/10/2019 Protocol Amendment Number: 4 Authors: A.B.,K.S.,L.L. Revision Chronology: 1) 8/10/2019 Original [COVID delay] 2) 4/21/2022 FDA recommended modifications from Q191165 incorporated to protocol: increased sample size to 60 opioid naïve acute (for 3 months) and 100 chronic (with 6 months followup); Replaced Sham with LG Smart TENS and added a blinding assessment; Outcome measures of PROMIS Pain Interference , Pain Intensity, Depression to be measured weekly the first month. 3) 6/8/2022 – Final survey design reduced daily diary reporting to 1 month due to budget constraints of longer follow up. Depression and Catastrophizing only as baseline; weekly NRS Pain Interference (3) PROMIS Pain Interference (2) and Pain Intensity collected until 3 months for all; Monthly surveys added past month NRS, Blinding assessment to monthly survey at 3 months and after for those started in chronic strata. Added "source" for each opioid use case to DOSE tool collecting opioid formulation, dose, and number of pills. 4) 5/5/23; Added "Do you think you will need surgery" and "do you think you will need epidural" questions, and "did you get surgery" and "did you get an epidural" to monthly. 5) 7/13/2023 New Location added

Funding	National Institute on Drug Abuse, R44DA049631, R44DA058952
Roles and Responsibilities	Principal Investigator: Amy Baxter MD, responsible for study design, overall project oversight, and compliance. Study Coordinator: Jena Slaski, responsible for daily operation, protocol adherence and patient coordination at Kaizo Health Centers. Lindsey Cohen assisted Dr. Baxter with initial study design, ongoing recruitment recommendations, pain measure decision-making, study flow creation. M. Louise Lawson PhD (Deceased), responsible for initial power analysis, statistical support for study design, revisions after FDA. Dr. Kevin Swartout PhD, responsible for programming of data collection instruments, ongoing support of data collection tool and dataset, database consolidation; Jessica Allia Williams PhD, responsible for statistical analysis of completed dataset. All apart from Dr. Lawson reviewed the manuscript.
Introduction	Low back pain (LBP) affects nearly 40% of adults, contributing to significant reductions in quality of life and productivity. The opioid epidemic, largely driven by prescriptions for pain, has created an urgent need for effective non-pharmacological pain treatments. Existing options such as TENS devices may provide acute relief, but are not available as an opioid substitute. A multimodal approach, combining mechanical stimulation, heat, cold, and acupressure, holds promise for reducing both acute and chronic pain and opioid prescribing.
Background and rationale for the study	Between 25 and 50% of patients presenting with acute or exacerbated chronic LBP (a/cLBP) receive prescriptions for opioids. ALBP progresses to chronic in 40% of those with moderate to severe pain (4 out of 10 on a 0 – 10 Numeric Rating Scale). Opioid pain relief is no better than placebo at 6 weeks after presentation, but increases the risk of cLBP and persistent use (5% of opioid naïve). Providing a multimodal low back pain device could reduce opioid prescribing or use compared to TENS; providing any device could reduce opioid prescribing and use compared to contemporaneous prescribing practices.
Objectives	**Primary Objective, Opioids:** To determine whether the use of a multimodal neuromodulatory mechanical stimulation (M-Stim) device (DuoTherm) can reduce opioids 30% compared to TENS in those with moderate to severe back pain.

	Co-Primary Objective, Acute Pain: To determine whether multimodal M-Stim reduces Pain Intensity 30% more than TENS in the first 10 days after presenting for treatment.

Co-Primary Objective, Chronic Pain: To determine whether multimodal M-Stim reduces disability 30% more than TENS at 6 months. |
Study Design	A randomized, double-blind controlled trial with 3- (aLBP) or 6- month (cLBP) follow-up.
Study Setting	The study will be conducted at mixed physical therapy/chiropractic practices in Washington, DC, Maryland, and Virginia, which offer demographic and economic diversity. These clinics provide an ideal environment, with frequent follow-ups and ongoing therapy but no on-site access to opioid prescribers.
Eligibility Criteria	**Inclusion Criteria**: - Male or female adults aged 18-90 presenting for treatment of acute or chronic low back pain - Self report of moderate to severe LBP of 4 or greater out of 10 on a 0-10 Numeric Rating Scale. - Acute: pain duration <3 months not using opioids for the current exacerbation of low back pain - Chronic: Pain duration >=3 months with or without ongoing opioid use - Capacity to understand risks and benefits (informed consent). - Smartphone for Qualtrics web-based platform use **Exclusion Criteria**: - Radicular pain likely reflecting a surgical or mechanical problem - Inability to apply or use the device - Sensitivity to cold or vibration (e.g Raynaud's or Sickle Cell Disease) - Diabetic neuropathy rendering a patient unable to determine if the device is too hot - New neurologic deficits, skin lesions over the low back area - A contraindication to any medication for pain management that would impact analgesic use record

	- Pacemaker
Intervention	The experimental arm DuoTherm is a novel multimodal low back pain relief device incorporating 8 harmonic vibration patterns of mechanical stimulation (M-Stim) including neuromodulatory frequencies, 5 intensity levels, and optional heat, cold, and pressure delivered through a sculpted metal plate attached with a belt and controlled by buttons on the belt. Patients will be instructed to use the device at least daily for 30 minutes. The active control is a prescription 4-lead 8-channel TENS unit (LG Smart) with variable intensity. Participants will be instructed to use the device for a minimum of 30 minutes a day. Both M-Stim and LG Smart TENS groups will receive a standard pain management regimen typically used for low back pain standardized across all clinicians participating in the study. Participants will keep the devices and be instructed to use them for pain as needed during the duration of the study.
Outcomes	**Opioid Use Primary Outcome:** Prior use: For patients with prior or ongoing opioid use, a 30% reduction in MME (Milligram Morphine Equivalents) between the first 14 days and the last 14 days of daily diary recordings using the DOSE data collection tool. Opioid naïve: 30% reduction of those receiving an opioid prescription "prescribed to me for this event" **Secondary outcomes:** Use days; total MME and use past 7 days in the opioid naïve; use days by those with more severe pain using the NIH Research Taskforce definitions; and prescribing compared to a contemporaneous national LBP population (25%). **Pain Primary Outcome:** Chronic**:** 30% lower disability at 6 months using PROMIS Pain Interference for those with ongoing pain >3 months Acute: 30% lower NRS 0-10 "pain now" from entry to 10 days for those presenting with an episode of pain starting within the past 2 weeks **Secondary Outcomes:** Change in disability for those with >=57.7 PROMIS Pain Interference; restoration of function to normal (PI=50);

		Initial Visit	Daily x 28 days	Weekly for 3 months	Monthly for 3 months	Monthly 4 - 6 months
Participant Timeline	Consent, Enrollment, Randomization	ALBP, CLBP				
	Minimum Dataset, Pain Catastrophizing Sullivan, PROMIS Depression, Physical Function	ALBP, CLBP				
	NRS (at that moment & past 24 hours)	ALBP, CLBP	ALBP, CLBP	ALBP, CLBP	ALBP, CLBP	CLBP
	NRS after 30 minutes	ALBP, CLBP				
	NRS Past week			ALBP, CLBP	ALBP, CLBP	CLBP
	NRS Past month				ALBP, CLBP	CLBP
	PROMIS Pain Intensity, Pain Interference	ALBP, CLBP		ALBP, CLBP	ALBP, CLBP	CLBP
	Dose, Opioid formulation, number Source (DOSE tool), other analgesics	ALBP, CLBP	ALBP, CLBP	ALBP, CLBP	ALBP, CLBP	CLBP
	Device usage		ALBP, CLBP	ALBP, CLBP	ALBP, CLBP	CLBP

(Top cell of table, continued from previous page: integrated analysis with common criteria for restoration of function with multifidus stimulation surgery.)

Sample Size	To estimate the M-Stim intervention effect size, a retrospective study of 59 cLBP patients on chronic opioids (100% prolonged opioid use) reported a 28% reduction in MME after spinal stimulator implantation,[40] reducing MME 26.2(SD32.8) compared to 5.8(SD34.2) for those with conventional treatment (effect size 0.60. A priori, we would be able to detect an effect size of 1 (meaning a difference of 1 standard deviation) with 94% power and alpha of .03 using a Wilcoxon Mann Whitney test with 30 in each group. With this effect size for a two-sided significance of 0.05, 17 participants per group would detect a 30% prescribing reduction, while 50 participants on chronic opioids per treatment group would provide 85.4% power to detect a 30% reduction in MME. Given the 20% in a previous study by Jamieson et al, we increased the cLBP sample to 50 in each group.

	We planned to recruit 60 aLBP participants who had never taken opioids for their back pain, and 100 cLBP without a new prescription but with or without chronic opioid for cLBP.
Recruitment	Patients were recruited from Kaizo Health Centers in Landover and Fairfax, through direct referrals, flyers, and digital content like social posts and emails targeting local populations. Flyers were also distributed at three local pain clinics.
Randomization	After eligibility screening and informed consent, a 4-digit participant ID and the intervention allocation were randomly assigned by the survey software to either the DuoTherm or LG Smart TENS group within acute and chronic arms. A copy of the informed consent was emailed to the participant.
Blinding (masking)	Participants were blinded to which device powered the study hypothesis, and blinded to their assigned intervention until after documenting initial NRS pain intensity. Success of blinding the study device (M-Stim) versus the active control (TENS) was tested at months 3-6 with prompts, "select which group you think you were in (control or treatment)" and "How confident are you (0 = Least Confident ... 100 = Most Confident)." The protocol statistician and study coordinator knew the intervention assignments during enrollment but did not conduct statistical analysis. The PI and treating chiropractor were blinded to allocation during enrollment, with the PI accessing data only after study completion. The analyzing statistician was blinded to device assignment until completion of data cleaning and initial analysis.
Data Collection Methods	Site coordinators entered identification and contact information after informed consent on a tablet, then recorded weight, height, and duration to confirm acute or chronic follow-up duration, then participants took the tablet to record pain intensity on a 0-10 NRS now and past 24 hours. While using the device for 30 minutes, participants completed 7-day pain intensity NRS, NIH Back Pain Research Minimum Dataset, including PROMIS measures of Physical Function, Pain Interference, Depression, and Catastrophizing via the Sullivan Catastrophizing scale, Injury Mechanism, prior treatments, exercise and athletic status. Participants were prompted to record analgesic use, pain, and device use daily for a month on the web-based platform, then weekly, with the monthly surveys adding Pain Interference. All surveys asked about

	analgesic use. Due to the anticipated heterogeneity of opioid formulations, a skip-logic data collection instrument algorithm was created with robust options for Dose per pill (34), Opioid formulations, e.g. hydrocodone, hydromorphone etc. (15) and the Source (DOSE tool, Supplement 2). Sources included "prescribed to me for this event", "prescribed to me for another event", "given to me by a family member", "given to me by a friend", "given to me by an acquaintance or stranger", or "purchased from someone without a prescription". These were converted to a total milligram morphine equivalent (MME) for analysis.
	Participants recorded when they used their device, duration of use, and any additional pain relief modalities (exercise, stretching, bath, hot tub, therapy, massage). Patients were asked to record any thermal use or therapy cycle or channel as appropriate to their device.
	Participants verbally endorsing pain for less than three months (acute) were entered into a 3 month follow-up program, or 6 months (chronic) for those for whom back pain had been an ongoing problem for more than 3 months.
Statistical Methods	Statistical analysis was performed with masked intervention allocation by a statistician new to the project to determine differences in primary and secondary outcomes.
	An intention-to-treat analysis included all participants meeting inclusion criteria. Summary statistics (means, standard deviations, proportions) were calculated using T-tests and Chi-squared tests. Opioid prescribing differences were calculated with raw percent of change and relative risks. Diary entries and item-level data were analyzed for missing data to assess the need for imputation. Relative risks were calculated for MME and opioid use days between intervention groups, with paired T-tests used to compare first two and last two weeks of MME in those who used opioids during the study. A linear regression assessed BMI's interaction with opioid use, calculating marginal effects with standard errors via the Delta Method. Data analysis was performed using STATANow/SE 18.5.
	For pain outcomes, in addition to the above methods, missing 10 day NRS-1 data will be imputed using forward fill and KNN. A neural network will be created to determine factors contributing to 13 week Pain Interference, with iterative modeling to reduce mean absolute error. Graphs with r-squared for predictors will be generated.

Data Monitoring	Data collection was conducted through an app that tracked daily pain, opioid use and device usage. Monitoring included weekly enrollment review by the protocol statistician to assess comprehension of the data collection tool. Adverse events were reported as per protocol. Obtained data was stored on password-protected network drives made accessible solely to the listed investigators. Data analysis will only be conducted in secure rooms with restricted access. These rooms will only be accessible to investigators. Patient samples will not be obtained. The Institutional Review Board reserves the right to audit any research files to assure the quality of any data used in this research
Safety/Harm	Q191165/S001 FDA ruled Non-significant Risk 18-Sept 2019. Risks are minimal, similar to those associated with a handheld massager or standard heat/cold therapy. Patients will be screened for sensitivity to cold or vibration. Any significant adverse events will be reported to the IRB and NIH within 24 hours. Device-related adverse events will be documented and reported.
Auditing	Periodic auditing will be conducted by the Institutional Review Board (IRB) to ensure compliance with protocol and safety regulations, and by site visits by the PI.
Ethics Approval	This trial has received ethics approval from the Kaizo Clinical Research Institute IRB and is registered under NCT04491175.

Protocol Amendments	Revision Chronology:
	
	  1) 8/10/2019 Original
	[COVID delay]
	
	  2) 4/21/2022 Incorporated FDA recommended modifications from Q191165 incorporated to protocol: increased sample size to 60 opioid naïve acute and 100 chronic (with 6 months followup); Replaced Sham with LG Smart TENS active control with 8 pre-programmed patterns to correspond with 8 pre-set DuoTherm therapy cycles and added blinding assessment. Outcome measures of PROMIS Pain Interference , Pain Intensity, Depression to be measured weekly the first month. We extended the follow-up from one week for acute pain to 3 months for acute pain and 6 months for chronic pain.
	  3) 6/8/2022 – Final survey design reduced daily diary reporting to 1 month due to budget constraints of longer follow-up. Depression and Catastrophizing only as baseline; weekly NRS Pain Interference (3) PROMIS Pain Interference (2) and Pain Intensity collected until 3 months for all; "Past month NRS" added to

	monthly surveys added past month NRS, Blinding assessment for additional 3 months for those started in chronic strata.
	Added "source" for each opioid use case to DOSE tool collecting opioid formulation, dose, and number of pills.
	We intended to use evaluate change in MME over time for chronic opioid users. The FDA recommended requiring participants on opioids maintain dosage and frequency. As we did not have access to prescribing records, and opioid reduction was a desired outcome measure, we evaluated opioid use for the first two weeks versus the last two of those endorsing prior opioid use. We extended the baseline and follow-up Pain Intensity measurements to one month rather than one week.
	3a) 8/31/22 – Site Visit. PI noted staff using "will not fit" criteria rather than BMI of 30 from pilot study. New device fits variable BMI, based on abdominal girth. Retained "if device fits", exclusion criteria using BMI changed to BMI >50, noting controversy in using BMI as exclusion criteria.
	4) 5/5/23; Added "Do you think you will need surgery" and "do you think you will need epidural" questions, and "did you get surgery" and "did you get an epidural" to monthly.
	5) 7/13/2023 New Location added
	Stratification by chronicity versus opioid use status: enrollment strata were based on verbal endorsement of duration and no acute opioid use for back pain. Initial evaluation of registration data after enrollment was complete revealed 16 of 60 in the "acute" strata reported a duration longer than three months, and half in each chronicity strata no prior opioids for LBP. In consultation with Clinical Trials.gov, we pooled the data and included both opioid and pain outcomes as a single NCT04491175 registry with two different publications and analyses.
Informed Consent	Informed consent will be obtained from each participant after screening. Participants will be informed about the voluntary nature of the study, with a HIPAA form for confidentiality. Consent will be documented via selecting 'continue' on the digital consent form.
Confidentiality	Patient data will be stored on password-protected network drives. All data will be de-identified using a unique study ID for each participant. Confidential records will be stored in secure, restricted-access rooms.
Declaration of interests	The principal investigator has financial conflict of interest from design and research into the DuoTherm device, and creating a company to

	develop the device with NIH SBIR funding. The collaborators declare no financial or personal conflicts of interest related to this study.
Dissemination Policy	Results will be disseminated through peer-reviewed journals, conferences, and possibly through NIH publications, ensuring that both positive and negative outcomes are reported.
Ancillary and Post-Trial Care	Patients will receive standard care post-trial and may keep their devices if found beneficial. Participants will be provided referrals for ongoing care as needed.
Publication Plan	High impact journal, with presentation at the IASP or similar pain-related conference.