Official Title:

Impact of Bridge™ device as a non-pharmacological approach to treat opioid withdrawal in opioid use disorder (OUD) subjects in an inpatient treatment center

DENE0001

Date of Protocol:

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Clinical Investigation Title:	Impact of Bridge™ device as a non-pharmacological approach to treat opioid withdrawal in opioid use disorder (OUD) subjects in an inpatient treatment center
Clinical Investigation Number, Version:	1.0
Other Study Identifier:	DENE0001
Study Device(s):	Bridge™ Active and Sham devices
Sponsor:	Masimo Corporation 52 Discovery Irvine, California 92618 USA

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1. INVESTIGATOR PAGE

Principal Investigator: [redacted]
Co-Investigator(s):

Investigation Site(s): [redacted]
Address:

IRB: WCG IRB
Address: 1019 39th Ave., SE
Suite 120
Puyallup, WA 98374

Agreement between Investigator and Sponsor Regarding Responsibilities for Good Clinical Practice

Sponsor and Investigator agree to comply with International Conference of Harmonization (ICH) E6 Good Clinical Practice guidance. 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 Clinical Investigation Plan.
- 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 ensure existence and record of all necessary compliance documents and will conduct monitoring visits to ensure appropriate conduct of the study. The principal investigator's signature on this page constitutes the investigator's affirmation that he or she is qualified to conduct the clinical investigation, agreement to adhere to all stipulations of this clinical investigation plan, the conditions of the Institutional Review Board (IRB) or Research Ethics Committee (REC) approval, federal and local regulatory requirements, 21 CFR 812, ISO 14155, and International Conference on Harmonization Good Clinical Practice (ICH GCP) guidance.

Principal Investigator: [redacted]	**Title:** [redacted]	**Signature:**	**Date:**
Sponsor Representative: [redacted]	**Title:** [redacted]	**Signature:**	**Date:**

2. OVERALL SYNOPSIS OF THE CLINICAL INVESTIGATION

Clinical investigation title:	Impact of Bridge™ device as a non-pharmacological approach to treat opioid withdrawal in opioid use disorder (OUD) subjects in an inpatient treatment center
Study objective(s):	The purpose of this prospective study is to investigate the efficacy of the Bridge™ device in reducing the symptoms of opioid withdrawal in a blind comparison to a sham device.
Investigational device(s):	Bridge™ active and sham devices
Number of subjects:	48 total subjects
Inclusion criteria:	• Participant able to provide written informed consent • Participant is 18 to 65-years old • Participant has confirmed opioid use disorder (OUD) as defined by the *Diagnostic and Statistical Manual of Mental Disorders-5* Participants is entering an OUD treatment program
Exclusion criteria:	• Participant requires tapering from another substance at entry to treatment • Participant is pregnant or lactating • Participant has a history of hemophilia or psoriasis vulgaris • Participant has a cardiac pacemaker implant device • Participant has irritated or broken skin at the site of intended device placement • Participant is currently participating in, or was enrolled in another clinical trial within the last 30 days • Participant has a history of poor wound healing • Participant has a severe autoimmune disease or uncontrolled diabetes • Participant has an open wound/abscess infection/MRSA • Participant has a history of a chronic pain in the last 90 days • Participant has a serious medical condition which in the judgment of the principal investigator or his/her designee would make study participation unsafe, or would make intervention compliance difficult • Participant has a psychiatric illness (bipolar disorder, schizophrenia, or other psychotic disorder, active suicidal ideation with a plan within the last month or suicide attempt)
Groups and Randomization:	Two groups randomized at enrollment Group 1: Interventional arm - Active device Group 2: Control arm - Sham device
Duration of the clinical investigation:	2 years for enrollment completion
Study endpoint(s):	PRIMARY: • Assess change in *Clinical Opiate Withdrawal Scale (COWS)* score SECONDARY: • Assess change in *Subjective Opiate Withdrawal Scale (SOWS)* score [redacted]

[redacted]

3. DESCRIPTION OF THE INVESTIGATIONAL DEVICE

Bridge™ is a small electrical percutaneous nerve field stimulator device that contains a battery-powered chip and wires that are applied around a subject's ear. It is an FDA-cleared[1], drug-free, non-surgical device that uses neuromodulation to aid in the reduction of symptoms associated with opioid withdrawal through stimulation of branches of cranial nerves V (Trigeminal), VII (Facial), IX (Glossopharyngeal), X (Vagus) and the occipital nerves.

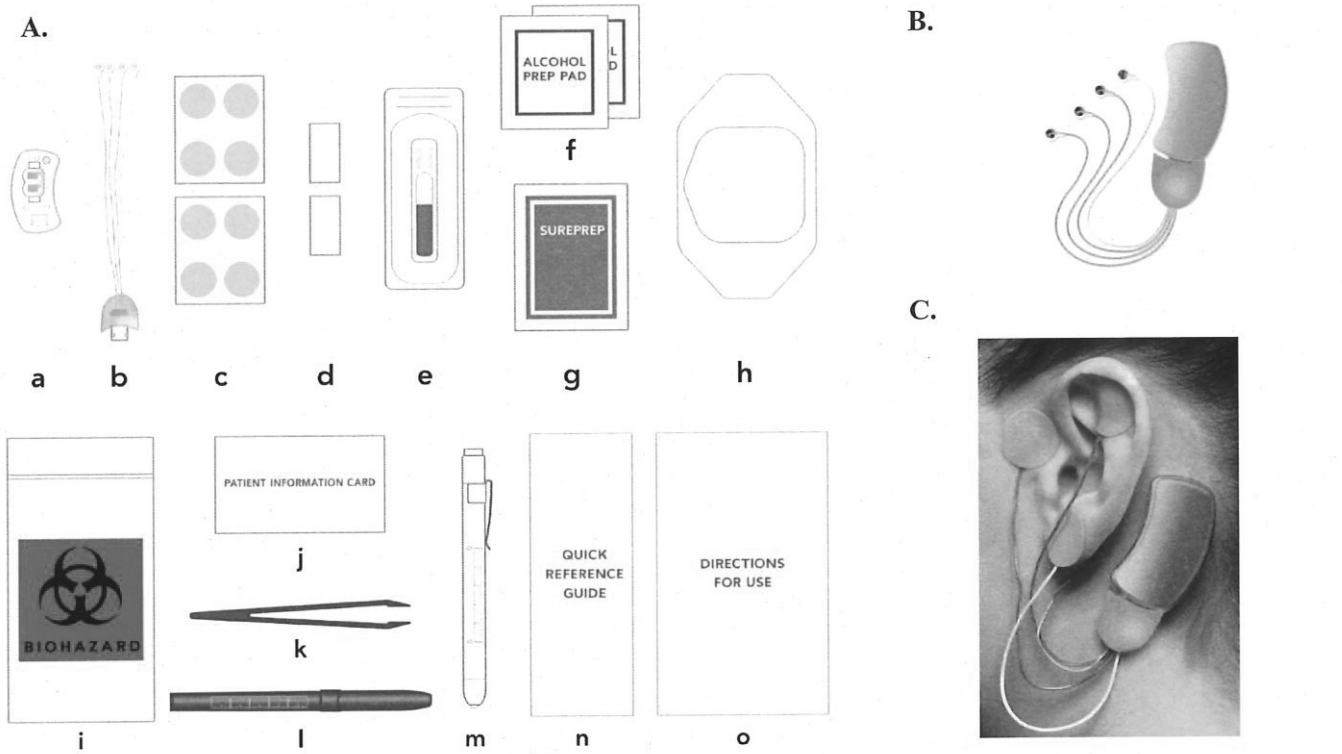


Figure 1. Overview of Bridge™ System. **A.** Bridge™ kit. The kit contains all items required for device placement which includes: a. Stimulator with inserted but not activated batteries, b. wire harness for use with the stimulator, c. eight round bandages, d. two stimulator adhesive, e. compound benzoin tincture, f. two alcohol swabs, g. Sureprep® protective wipe, h. Tegaderm™, i. biohazard bag, j. patient information card, k. tweezer, l. surgical marker, m. transilluminator/medical light, n. *Quick Refrence Guide*, o. *Directions for Use*. **B.** Bridge™ device. The device is composed of the stimulator which is the power source of the device and placed behind the ear and the wire harness with four electrodes to be placed on different zones of the ear for stimulation. **C.** Bridge™ device worn by a patient.

The main components of the Bridge™ device are the Bridge stimulator (Fig. 1. A. a.), which is the power source of the device and the wire harness (Fig. 1. A. b.), which transmits the signal to the attached arrays. The kit includes the following additional items required for proper placement, securement, and disposal of the device:

- Eight round bandages to place over the arrays and secure the appliance leads (Fig. 1. A. c.)
- Two stimulator adhesives used to affix the stimulator to patient skin (Fig. 1. A. d.)
- Compound benzoin tincture, which is a disinfectant and adhesive used to keep the implanted electrodes in place, avoiding array migration (Fig. 1. A. e.)
- Two alcohol swabs to clean and disinfect the skin of any oils and makeup (Fig. 1. A. f.)
- Sureprep® protective wipe to help protect skin and aid adhesion (Fig. 1. A. g.)
- Tegaderm™ for additional coverage of stimulator and wires if need (Fig. 1. A. h.)
- Biohazard bag for device disposal (Fig. 1. A. i.)
- Patient information card (Fig. 1. A. j.)
- Disposable tweezers to hold array for implantation (Fig. 1. A. k.)
- Surgical marker used to mark transplantation sites (Fig. 1. A. l.)
- Transilluminator to visualize and isolate the neurovascular bundles for proper array placement (Fig. 1. A. m.)
- *Quick Reference Guide* (Fig. 1. A. n.)
- *Direction for Use* (Fig. 1. A. o.)

As shown in Figure 1.C, the Bridge™ wire harness has four wires: three gray wires with single-pin electrodes and one white wire with a multi-pin array, which serves as a ground wire. Two of the single-pin electrodes and the multi-pin electrode are placed on the front (ventral) of the ear and one single-pin electrode is placed on the back (dorsal) of the ear. The stimulator is placed behind the ear and percutaneous electrodes are positioned using the transilluminator. The use of transillumination is necessary to locate, visualize, and isolate the auricular neurovascular bundles. The medical marker can then be used to mark the final locations of implantation of the electrode arrays. Implantation sites of the electrodes should not be directly over a large arterial branch but rather within 1 mm to avoid bleeding. This assures maximum energy transfer, minimum tissue resistance, and minimizes patient discomfort. As shown in Figure 2, the first electrode implantation zone is the ear lobe (lobule) for the multi-pin ground electrode. The second zone is anterior and superior to the tragus, which allows for the simultaneous stimulation of the Trigeminal nerve and a branch of the superficial temporal artery. The third zone is the superior one-third ventral aspect of the ear (anterior scaphoid fossa). The fourth and final zone is the dorsal aspect of the ear (posterior aspect of the helix) which covers large branches of the posterior auricular artery leading to the external ear. The Bridge device has a 120-hour runtime and has a pulse sequence of 2 hours on and 1 minute off with the cycle repeating over the 120-hour runtime. The sham device is similar to the active device, except that the stimulator does not deliver any current.

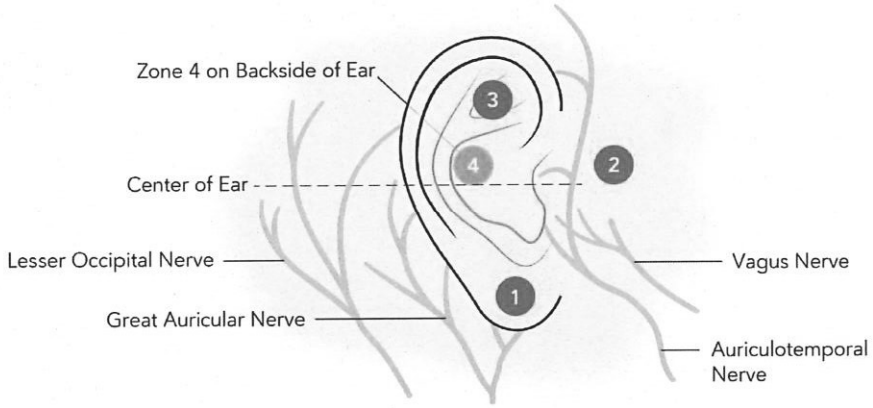


Figure 2. Overview of Bridge™ Placement. **Zone 1**. Great Auricular Nerve. Implantation of multi-pin array in the center of the ear lobe. **Zone 2.** Auricular Branch of the Vagus Nerve. Implantation of one of the single-pin electrodes in the area anterior and superior to the tragus. **Zone 3.** Auriculotemporal Nerve. Implantation of the next single-pin electrode at the superior one-third ventral aspect of the ear. **Zone 4.** Lesser Occipital Nerve. Implantation of the last single-pin electrode at the dorsal side of the triangular fossa.

Refer to Investigator Brochure and User's Manual for complete device instructions and descriptions.

4. JUSTIFICATION FOR CLINICAL INVESTIGATION DESIGN PLAN

Opioid addiction is a serious public health issue that negatively impacts many communities around the world. Opioid use (including prescription opioids and heroin) kills many people in the U.S. each year. From 1999 to 2018, opioids were involved in more than 446,000 deaths[3], approximately 232,000 of which were the result of overdoses related to prescription opioids.[4] In 2018, the most recent year for which data is available, approximately 47,000 deaths involved opioids, almost 15,000 of which involved prescription opioids.[3]

The current standard of care treatment for patients suffering from OUD is participation in a medication assisted treatment (MAT) program. However, one of the obstacles of reaching to an MAT program is the fear of enduring opioid withdrawal symptoms associated with the abrupt discontinuation of opioid use during the detoxification phase. Acute opioid withdrawal is often accompanied by painful, often severe flu-like symptoms including but not limited to sweating, gastrointestinal upset, tremors, anxiety, agitation, insomnia, and joint pain lasting for up to two weeks. Accordingly, voluntary discontinuation by opioid users is a long and challenging process. It has been estimated that less than 20% of the more than two million people suffering from OUD in the U.S. are receiving treatment.[5]

Bridge™, which received FDA clearance in 2017 and aids in relieving opioid withdrawal symptoms, may be the solution to helping individuals who suffer from OUD. A 2018 study by Miranda and Taca,[5] in a cohort of 73 OUD individuals during the induction phase of opioid withdrawal, demonstrated that Bridge™ reduced acute opioid withdrawal symptoms within 15-30 minutes and provided continuous relief for the duration of five days of device wear. In this study, withdrawal symptom evaluated through comparison of *COWS* scores at various time points after device placement to baseline showed 84.6% reduction in *COWS* after the first hour of Bridge™ use and 97.1% after five days.[5] By aiding in the reduction of withdrawal symptoms, Bridge™ has the potential to help OUD patients with successfully transitioning away from opioids and into an appropriate treatment plan.

[redacted]

The intent of this study is to investigate the efficacy of Bridge™ in alleviating withdrawal symptoms in a prospective, sham-controlled setting. *COWS* and *SOWS* will be used to assess the severity of opioid withdrawal symptoms and as an outcome measure to assess treatment effect. *COWS* is a validated, clinically relevant, and reliable objective measure of therapeutic effect and clinical benefits, which is widely used in drug treatment protocols to assess the signs, symptoms, and severity of acute withdrawal, while *SOWS* is a subjective measure [6, 7]. [redacted]

5. BENEFITS AND RISKS OF THE INVESTIGATIONAL DEVICE, CLINICAL PROCEDURE, AND CLINICAL INVESTIGATION

Anticipated benefits: There may be direct benefits to subjects participating in the active Bridge™ arm. There are no anticipated benefits to subjects who receive the sham device.

Device risks: Potential risks of percutaneous therapies, generally, include bleeding or infection at the puncture site, pain or skin irritation at the application site. Refer to the *Instructions for Use* for safety information, warnings, and cautions.

Contraindications: The device is contraindicated for use by patients with cardiac pacemakers, hemophilia, and psoriasis vulgaris. 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 electrodes to the ear.

Risk mitigation: Device shall be placed on intact skin only and subjects with cardiac pacemakers, hemophilia, and psoriasis vulgaris will be excluded from the study.

6. OBJECTIVES OF THE CLINICAL INVESTIGATION

The purpose of this prospective study is to investigate the efficacy of the Bridge™ device in reducing the symptoms of opioid withdrawal in a blind comparison to a sham device.

Primary hypothesis:

- Participants on the active Bridge™ device will show significant reduction in the severity of opioid withdrawal signs and symptoms, assessed using the *COWS* score, in comparison to the sham group.

Secondary hypothesis:

- Participants on the active Bridge™ device will show significant reduction in the severity of opioid withdrawal signs and symptoms, assessed using the *SOWS* score, in comparison to the sham group.

[redacted]

[redacted]

7. DESIGN OF THE CLINICAL INVESTIGATION

7.1. General

This is a two-arm, prospective, randomized, double-blind, sham-controlled clinical trial. The sham control device will be identical in appearance to the active device but will not deliver electrical current. Enrolled participants will be randomly assigned an active of sham Bridge™ device based on the randomization scheme provided by the sponsor. Sponsor will sequentially number devices to ensure allocation concealment. Research staff placing the device will not collect data on the CRF for that subject to prevent any bias in data collection. Unblinding of participant's treatment assignment will only be broken if the health of the participant is at risk as determined by an onsite medical doctor.

Overview of tasks to be completed

1. Prescreening, consenting, eligibility verification, demographic, medical history data collection
2. Baseline assessments *(COWS, SOWS,* [redacted]*)*
3. Randomization and Bridge placement
4. Assessments throughout the course of the study (See Table 1)
5. Study Follow-Up

7.2. Endpoints

Primary endpoints:

- Assess change in *Clinical Opiate Withdrawal Scale (COWS)* score

Secondary endpoints:

- Assess change in *Subjective Opiate Withdrawal Scale (SOWS)* score

[redacted]

[redacted]

7.3. Investigator Site

This will be a single center study at the following location:

[redacted]

7.4. Investigational Device(s) and Comparator(s)

Bridge™ is an FDA-cleared medical device for the treatment of symptoms related to opioid withdrawal. Participants will be assigned to one of two interventions: active device or sham device. The sham device will be identical in appearance to the active device but will have no electrical current.

7.5. Participants

7.5.1. Inclusion Criteria

- Participant able to provide written informed consent
- Participant is 18 to 65-years old
- Participant has confirmed opioid use disorder (OUD) as defined by the *Diagnostic and Statistical Manual of Mental Disorders-5*
- Participant is entering an OUD treatment program

7.5.2. Exclusion Criteria

- Participant requires tapering from another substance at entry to treatment
- Participant is pregnant or lactating
- Participant has a history of hemophilia or psoriasis vulgaris
- Participant has a cardiac pacemaker implant device
- Participant has irritated or broken skin at the site of intended device placement
- Participant is currently participating in, or was enrolled in another clinical trial within the last 30 days
- Participant has a history of poor wound healing
- Participant has a severe autoimmune disease or uncontrolled diabetes
- Participant has an open wound/abscess infection/MRSA
- Participant has a history of a chronic pain in the last 90 days

[redacted]

- Participant has a serious medical condition which in the judgment of the principal investigator or his/her designee would make study participation unsafe, or would make intervention compliance difficult
- Participant has a psychiatric illness (bipolar disorder, schizophrenia, or other psychotic disorder, active suicidal ideation with a plan within the last month or suicide attempt)

7.5.3. Point of Randomization

After verification of eligibility, participants will be randomly assigned to one of the two groups of active or sham in equal ratios. The randomization table will be kept with the sponsor.

7.5.4. Participant Classifications

Participants will be classified according to the criteria below:

- **Screened** – Participants who are assessed for study eligibility after signing informed consent.
- **Enrolled** – Clinical trial participants who have met all inclusion criteria and do not meet any exclusion criteria and have been assigned a participant identification number.
- **Screen Failure** – Participants who do not meet all eligibility criteria. (Reason of the participant's ineligibility will be documented on a *Screening and Enrollment Log*).
- **Withdrawn** –Participants 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. If a participant leaves the study prematurely or is withdrawn from the study, another participant may be recruited.
- **Lost to Follow-up** – Participant is unable to be reached for follow-up after 3 attempts. Research staff shall document on the CRF, and no further attempts will be made.
- **Completed** – Participants will be considered complete if they wear the Bridge™ for 5 days.

7.6. Study Procedures

7.6.1. Recruitment and Consent

Patients [redacted] upon arrival to the center will be approached and consented. The Bridge™ device will be placed immediately on the participant prior to providing comfort medications.

[redacted]

The informed consent document will explain that comfort medications may be delayed until the Bridge is placed, as long as the participant is willing to do so. [redacted]

The Investigator and/or staff delegated for this task are responsible for conducting the informed consent process and for obtaining written informed consent prior to each participant's inclusion into the study. Subjects must provide written or electronically signed informed consent, as approved by the IRB, prior to being enrolled in the study, in accordance with applicable federal and provincial regulations.

Following identification of a potentially eligible subject as defined by the inclusion and exclusion criteria, the subject will be approached by research staff who will thoroughly explain the purpose, procedures of the study in respect to subject's involvement and responsibilities, potential risks and benefits, and 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.

Subjects will be given adequate time to read the informed consent form and ask questions regarding the study. Once all questions have been answered and the informed consent has been signed, the subject will be enrolled in the study. If the subject declines to participate, they will not be enrolled in the study.

The Investigator shall retain a copy of the signed informed consent document in each subject's record. All paper-based signed consents will be kept at the site and are only accessible to study team members. A copy of the signed consent and HIPAA/data protection authorization will be provided to the subject. The Investigator is also responsible for ensuring any new information which may affect the subject's health, welfare, or willingness to stay in the study will be provided to the subject. Subjects may need to be re-consented to continue participation if required by IRB.

7.6.2. Verification of Eligibility, and Participant Demographics

The Investigator and/or staff delegated for this task shall conduct screening assessments to verify eligibility criteria for the subject. If the subject does not meet all eligibility criteria, they will be notified and considered a screen failure.

Research staff will collect and record on the CRF the participant's demographic information, including but not limited to; age, self-identified; gender, race & ethnicity. Medical History will also be recorded on the CRF.

7.6.3. Allocation Concealment and Randomization

[redacted] A block randomization algorithm will be utilized to generate the random allocation list. Participants will be randomly assigned to one of the two groups of active or sham in equal ratios.

7.6.4. Blinding and Unblinding Rules

A randomization table will be kept with the sponsor. Subjects and study site staff (investigators, researchers, care providers) will be blinded to the group assignment. Personnel involved in device placement will not be involved in subject care or study outcome data collection to avoid any potential bias. Should a subject experience an adverse event and the investigator deems unblinding necessary for appropriate care, the subject and research staff will be unblinded and the subject will be withdrawn from the study.

7.6.5. Assessments

Delegated research staff will administer the *COWS* [redacted] and provide the patient with the *SOWS* [redacted] assessments to complete. Personnel involved in device placement will not administer the assessments to avoid any potential bias. Refer to Table 1 for time and frequency of assessments. Demographic information (i.e., age, gender, race, etc.) will also be collected and recorded on the CRF.

The instruments that will be used are listed below. Any changes to the listed assessments will be noted in the study records.

Clinical Opiate Withdrawal Scale (COWS): *COWS* is an 11-item clinician administered scale used for measuring opiate withdrawal signs.[6] The COWS takes approximately 2 minutes to complete. See Appendix I.

Subjective Opiate Withdrawal Scale (SOWS): *SOWS* is a self-reported rating scale measuring the experience of 16 symptoms on a Likert scale from 0 (not at all) to 4 (extremely).[7] See Appendix II.

[redacted]

7.6.6. Device Placement

[redacted]

The ear shall be cleaned with alcohol wipes and transilluminated to mark the vascular branches. The needles shall be placed in the dorsal and ventral aspects of the ear within 1–1.5 mm of the vascular branches, but not on main arterial branches. The generator will be attached with adhesive to the skin behind the ear just over the mastoid process. A photograph may be taken immediately after device placement to use as a reference for where the leads should be. No identifying features shall be captured on the photograph.

7.6.7. Symptom Control Medications

Symptom control medications such as phenobarbital, clonidine, cola syrup, melatonin, ibuprofen, promethazine, dicyclomine, loperamide should not be provided for 2 hours after Bridge placement. If the subject requires symptom control medications within 2 hours of device placement, medications should be provided and recorded on the CRF.

7.6.8. Device Removal

Medical staff trained and delegated will remove the Bridge device on Day 6. The device shall be disposed in a Sharps container, in accordance with Masimo's Bridge Device Training program, the Device Instructions for Use (DFU) and Operator's Manual.

If subject requests to remove the Bridge device prior to 5 days, they will be withdrawn from further study assessments and procedures, however their data collected up to the point of withdrawal may still be used for data analysis.

7.6.9. Study Follow-Up

About two weeks after the patient leaves treatment, research staff will contact the participant to determine if they proceeded to the next level of care (i.e., day program, office-based opioid treatment, intensive outpatient program, etc.). Details about the program will be recorded on the CRF. If the participant is unable to be reached after three attempts, research staff shall document on the CRF. No further attempts will be made.

7.6.10. Study Completion

The subject is considered to have completed the study after they have worn the Bridge™ device for 5 days.

7.6.11. Study Duration

The study duration for each participant is expected to last about two weeks. The duration of the clinical trial enrollment is expected to last two years.

7.6.12. Schedule of Events

Study procedures will be conducted according to the schedule [redacted]

[redacted]

[redacted]

7.7. Monitoring Plan

Oversight for this clinical trial is provided by the sponsor, investigators, and local IRBs.

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 trained on departmental Standard Operating Procedures (SOPs) on conduct and monitoring of sponsored studies.

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 participant 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 initial enrollment, a visit when approximately 20 subjects have been enrolled, and approximately every 4-6 months thereafter.
- A final close out visit after the last participant had finished the study.

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 participant confidentiality is maintained in agreement with HIPAA regulations. The Investigator will provide the monitor access to all necessary records to ensure the integrity of the data (21 CFR 812).

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

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

After each visit, the monitor will provide a monitoring report to the Investigator within four weeks of visit completion. The monitoring report will detail findings and open action items observed during the visit. It is the responsibility of the PI 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.

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

8. STATISTICAL DESIGN AND ANALYSIS

This is a single site, two-arm, prospective, randomized, double-blind, sham-controlled clinical trial. The study's main outcomes are COWS and subjective opiate withdrawal scale (SOWS) scores, measured over 8 time periods: at baseline, 30, 60, 120 minutes, 2nd, 3rd, 4th, and 5th day.

The study design data results in correlated observations will be collected repeated measurements within clusters (i.e., patients). These correlations invalidate the independence assumption in commonly used univariate and multivariate statistical techniques such as t-tests and multiple linear regression. Therefore, the Generalized Estimating Equations (GEE) method was used to estimate the power and sample size, a flexible class of models that account for correlated observations and are a commonly used method for repeated data analysis. This class of model does not require the normality assumption and does not require the full specification of the joint distribution of repeated measurements. Further, the power/sample size for testing the time-averaged difference (TAD) between two means from continuous, correlated data that will be analyzed using the GEE method was calculated. Such data occur in two design types: clustered and longitudinal (repeated measurement). Time-averaged difference analysis is often used when the outcome to be measured varies with time.

The following parameter estimates are required for calculating the power:

1. Alpha (α): The probability of rejecting a true null hypothesis = 0.05
2. δ: The time-averaged difference at which the power is calculated. We estimated that the COWS time average is 2.8 for the Bridge group and 6.8 for the sham group, then $\delta = 4.0$.

   The *δ of 4.0* was selected such as to be conservative and taking into consideration:

- After the first two hours comfort medications and medication tapers may be administered to the control group thus the COWS score may be reduced
- After three days the withdrawal symptoms are anticipated to abate for both groups

The above rationale was discussed with and supported by Masimo Bridge device and OUD clinical experts.

The power was calculated for various TAD δ values 2.8, 3, 4 and 4.7 (see Figure 3).

3. σ: The standard deviation of a response (COWS): 5.047 (estimated, see Table 2 below).
4. ρ: The base correlation between two responses on the same subject. We used the estimate calculated by the other statistician for the sample size calculation (0.40).
5. The treatment group allocation proportion is the proportion of subjects that are in the treatment group. The proportion is 1:1 (50%)
6. The number of time points at which each subject is measured: 9.
7. The time values represent the proportion of the total study time that has elapsed just before the measurement: 0, 0.003, 0.005, 0.01, 0.021, 0.25, 0.5, 0.75, 1, which are equivalent to: prior to device placement, 20 min, 30 min, 60 min, 120 min, 2nd day, 3rd day, 4th day and 5th day.

Data used for the sample size calculation was abstracted from the article by Adrian Miranda & Taca (2018)[5].

Table 2. COWS Score Statistics Based on Article by Adrian Miranda & Arturo Taca (2018)[5]

	BRIDGE Group			
Time (mins)	Mean COWS	% Reduction	SD	n
0	20.1	0.0	6.1	73
20*	7.5	62.7	5.9	62
30	4.0	80.1	4.4	73
60	3.1	84.6	3.4	71
120	2.8	86.1	**	
1440 (Day 2)	2.1	89.6	**	
2880 (Day 3)	1.4	93.0	**	
4320 (Day 4)	1.0	95.0	**	
5760 (Day 5)	0.6	97.0		33
Average	2.8	86.0		
Pooled SD			5.047	

* 20 minutes measurement is not included in the study design; it was included from the article to enhance the estimates for the required parameters for the sample size/power calculations.
** The yellow highlighted values are estimated (extrapolated from the available data)

A sample of 32 subjects (16 in each group), each measured 9 times, achieve a power of 0.9068 when using a two-sided Wald test from a GEE analysis to test whether the time-average difference of the Bridge subjects differs from that of the sham subjects by more than 4.0 at a significance level of 0.05. The subjects are randomly split between a

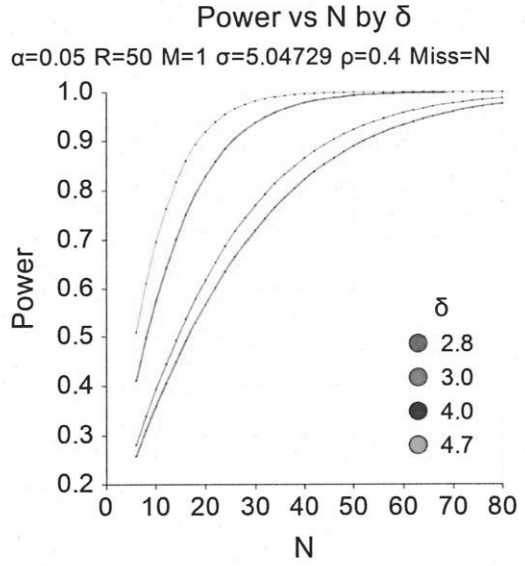
[redacted]

Bridge group and a sham group, with 50% of the subjects assigned to the Bridge group. The residual standard deviation is anticipated to be 5.04729. The measurements of each subject will be made at the following times expressed as proportions of the total study time: 0, 0.003, 0.005, 0.01, 0.021, 0.25, 0.5, 0.75, 1, which are equivalent to: prior to device placement, 20 min, 30 min, 60 min, 120 min, 2nd day, 3rd day, 4th day and 5th day. Missing values are assumed to occur completely at random (MCAR). [redacted]

Anticipating a 50% drop out and missing COWS evaluation rate, 48 participants (24 in each arm) should be enrolled into the study to guarantee a minimum of 32 participants who complete the COWS evaluation and the study.

Figure 3 below shows the relationships of power and sample size for the various δs.

Figure 3. Power versus Sample Size for δ of 2.8, 3.0, 4.0 and 4.7



A separate Statistical Analysis Plan has been developed for this study.

9. DATA MANAGEMENT

9.1. Data Management and Confidentiality

All documents associated with this protocol will be securely stored in a physical location or on password-protected computers. The confidentiality and retention of these documents will be protected to the extent provided and required by the law. All data will be de-identified before any statistical analysis. Only de-identified data will be shared with Masimo for research purposes stated in this protocol. Data collected by the eCRF data capture software will be shared with Masimo via a secure, password-protected server that only research staff, and Masimo study team members will have access to. Data will be retained for a minimum of two years following completion of the final analysis.

[redacted]

9.2. 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.

9.3. Case Report Forms

The site shall capture study data in case report forms (CRFs) for each subject enrolled, to be provided to the sponsor. CRFs may be in paper or electronic format through electronic data capture (EDC) software. Masimo shall ensure that systems used for electronic CRFs are compliant with the requirements of 21 CFR Part 11 and ISO / IEC 27001 certification. The CRFs will be completed and signed by the PI or delegate. This also applies to those participants who fail to complete the study.

If a participant withdraws from the study, the reason must be noted on the CRF. The eCRFs are to be completed on an ongoing (weekly) basis. CRF entries and corrections will only be performed by study site staff, authorized by the investigator. For paper CRFs, entries and corrections to the CRF will be made following good documentation practices (GDP).

The CRF may include the following information, including but not limited to: inclusion/exclusion criteria, whether participant consent was obtained before start of study, demographic information, device readings, and if occurrence of any adverse event, protocol deviation, and device deficiencies, etc. The CRFs will be signed by the PI or delegate to attest that the data are complete and accurate.

CRF entries will be checked by the study monitor and any errors or inconsistencies will be queried to the site on an ongoing basis. Any changes made within an electronic CRF will be tracked by audit trail. Any changes on a paper CRF will be made directly on the CRF and will be initialed and dated by the person making the change. Query resolution will be assessed and confirmed by study monitor during site visit.

9.4. Data Transfer and Storage

Original paper CRFs will be stored in a secure location at the site. Copy of the original paper CRFs may be scanned and sent to sponsor. If using electronic CRFs, the site staff will be assigned unique usernames and passwords for data security. Final copies of the electronic CRFs in EDC are stored on a secure server.

Only authorized sponsor personnel will have access to study data and will move it to a secure and backed-up drive at Masimo.

CRFs will be checked for completeness and if there are inconsistent or missing data points, queries will be generated. If delegated research staff are to correct the paper CRF, they shall follow GDP practices to strike through old entry, add in new entry, initial and date it, and provide the corrected information to sponsor. Corrections made to electronic CRFs will be tracked by audit trail and require PI or delegate sign-off.

9.5. Record Retention

Study data will be retained for the necessary period of time as required by the institution's regulations. Study records shall be retained for a minimum of two years after study closure. The institution's own retention policies and regulations may apply in addition to the minimal requirement.

10. AMENDMENTS TO THE CLINICAL INVESTIGATION PLAN

Any changes made to the clinical investigational plan/study protocol will be documented by way of an amendment. Before submitting a protocol amendment to the IRB, the protocol amendment must be agreed upon and signed by both the PI and the sponsor. The protocol amendment will be submitted to the IRB for approval. At a minimum, a redline version and a clean version of the new protocol amendment will be kept on file by the PI and the sponsor. Protocol amendments will need to be version controlled. Both PI and sponsor will retain the IRB approval letter as confirmation that the protocol amendment was approved.

11. DEVIATIONS FROM CLINICAL INVESTIGATION PLAN

Deviations from the protocol must receive both sponsor and the investigator's IRB/ethics committee approval before they are initiated, with the exception that under emergency circumstances, deviations from the *Clinical Investigation Plan* to protect the rights, safety and well-being of human participants may proceed without prior approval of the sponsor or the IRB/ethics committee.

Any protocol deviations initiated without sponsor and the investigator's IRB/ethics committee approval that may affect the scientific soundness of the study, or affect the rights, safety, or welfare of study participants, must be documented and reported to the sponsor and to the investigator's IRB/ethics committee as soon as a possible, but no later than 5 working days after the occurrence of the protocol deviation. In addition to documenting deviations on the CRF, the *Protocol Deviation Form* may also be used. If protocol deviations continue to occur frequently at a study site, a corrective and preventive action (CAPA) may be opened by the sponsor.

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 five working days of the IRB notification of withdrawal of approval.

12. DEVICE ACCOUNTABILITY

12.1. Receipt of Study Device

Upon receipt of the study device supplies, an inventory must be performed, and the device accountability log filled out and signed by the person accepting the shipment. It is important that the designated research 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.

12.2. Use of Study Device

Use of device will be documented in a CRF module for each participant. Any unused devices must be returned to the sponsor at the end of the study or before product expiration date.

12.3. Return or Destruction of Study Device

At the completion of the study, there will be a final reconciliation of study devices shipped, devices used, and devices remaining. 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 onsite will only be upon written instruction from the sponsor and will be documented in the study files. When a Masimo device deficiency is observed, every effort should be made to return the device and its packaging to the Sponsor in a timely manner.

13. STATEMENTS OF COMPLIANCE

This document is a clinical investigational plan for a human research study sponsored by Masimo Corporation. 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 the IRB or REC approval, federal and local regulatory requirements, 21 CFR 812, ISO-14155, ICH GCP guidance.

The protocol, ICFs, recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study.

14. ADVERSE EVENTS, ADVERSE DEVICE EFFECTS, AND DEVICE DEFICIENCIES

14.1. Definitions

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

- adverse event: untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in participants, users or other persons, whether or not related to the investigational medical device and whether anticipated or unanticipated (ISO 14155)
- adverse device effect: adverse event related to the use of an investigational medical device
- serious adverse event: adverse event that led to any of the following:
    - a) death
    - b) serious deterioration in the health of the participant, users, or other persons as defined by one or more of the following:
        - 1) a life-threatening illness or injury, or
        - 2) a permanent impairment of a body structure or a body function including chronic diseases, or
        - 3) in-participant or prolonged hospitalization, or

- 4) medical or surgical intervention to prevent life-threatening illness or injury, or permanent impairment to a body structure or a body function,

- c) fetal distress, fetal death, a congenital abnormality, or birth defect including physical or mental impairment

Note: Planned hospitalization for a pre-existing condition, or a procedure required by the *Clinical Investigation Plan*, without serious deterioration in health, is not considered a serious adverse event.

- serious health threat: signal from any adverse event or device deficiency that indicates an imminent risk of death or a serious deterioration in the health of participants, users or other persons, and that requires prompt remedial action for other participants, users or other persons.

  Note: This would include events that are of significant and unexpected nature such that they become alarming as a potential serious health hazard or possibility of multiple deaths occurring at short intervals.

- serious adverse device effect: adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event

- unanticipated serious adverse device effect: serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current risk assessment

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

- device deficiency: inadequacy of a medical device with respect to its identity, quality, durability, reliability, usability, safety or performance

  Note 1: Device deficiencies include malfunctions, use errors, and inadequacy in the information supplied by the manufacturer including labeling.

  Note 2: This definition includes device deficiencies related to the investigational medical device or the comparator.

14.2. List of Anticipated Adverse Events

Potential risks of percutaneous therapies, generally, would include bleeding or infection at the puncture site, pain at the application site, or skin irritation at the site of application. Refer to the Instructions for use for safety information, warnings, and cautions.

14.3. List of Non-Reportable Adverse Events

All adverse events that occur while the subject is wearing the device will be reported.

14.4. Adverse Event Reporting

- All adverse events, both anticipated and unanticipated, must be recorded in the within the CRF and in 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 five 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, participant hospitalization, severe or permanent disability or were life threatening, their relationship to the study device, and resolution.

14.5. Device Deficiencies Reporting

All Masimo device related deficiencies should be reported to the sponsor and must be recorded in the CRF in a timely manner. When a Masimo device deficiency is observed, every effort should be made to return the device and its packaging to the sponsor in a timely manner.

15. VULNERABLE POPULATION

15.1. Definition

Vulnerable population are research participants, such as children, prisoners, pregnant women, handicapped, or mentally disable persons, or economically or educationally disadvantaged persons, who are likely to be vulnerable to coercion and undue influence.

The federal regulations that govern the protection of human participants require additional protection for the vulnerable population.

15.2. Protection of Vulnerable Participants

- Reasonable compensation (i.e., travel expenses) may be provided for economically disadvantaged participants to eliminate the possibility of undue influence due to financial incentive.
- Educationally disadvantaged participants will be provided ample time to ask questions and comprehend information.
- Medical care will be provided to these participants after the clinical investigation has been completed 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.

15.3. Responsible Parties

- The IRB will review research with vulnerable populations and evaluate consent, level of risk, coercion, and the reason for choosing this particular participant 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 participants by ensuring that all regulations and proper documentation of consent are handled in a compliant and timely manner.

16. SUSPENSION OR PREMATURE TERMINATION OF THE CLINICAL INVESTIGATION

16.1. 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 participants.

If the sponsor determines that the study site's compliance to be inadequate at any point during the study, and the sponsor moves to suspend or terminate the study site, the sponsor will provide notification in writing to the PI 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 participant enrollment upon receiving written notification of reinstatement from the sponsor.

If for any GCP and Regulatory non-compliance reasons the study site is prematurely terminated by the sponsor, then the study site is not eligible for reinstatement under the same *Clinical Investigational Plan/Study Protocol.*

16.2. Termination of Clinical Investigation/Study Due to UADE

The clinical investigation may be terminated if the sponsor determines that an unanticipated adverse device effect presents an unreasonable risk to the participants. Termination shall occur no later than five 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.

17. PUBLICATION POLICY

In compliance with 42 CFR Part 11, a study that meets the definition of an Applicable Clinical Trial (ACT) and that is initiated after September 27, 2007, must be registered on ClinicalTrials.gov. Results of this clinical investigation will be made publicly available on the ClinicalTrials.gov website.

18. BIBLIOGRAPHY

1. FDA. FDA grants marketing authorization of the first device for use in helping people to reduce the symptoms of opioid withdrawal [News Release]. 2017
2. Wilson N et al. Drug and Opioid-Involved Overdose Deaths — United States, 2017–2018. MMWR Morb Mortal Wkly Rep 2020;69:290–297. DOI: http://dx.doi.org/10.15585/mmwr.mm6911a4.
3. Centers for Disease Control and Prevention. (2020, Dec). The Drug Overdose Epidemic: Behind the Numbers. Centers for Disease Control and Prevention, National Center for Injury Prevention and Control. https://www.cdc.gov/drugoverdose/data/prescribing/overview.html.
4. National Institute on Drug Abuse, Advancing Addiction Science. (2018, June). Medications to Treat Opioid Use Disorder Research Report: Overview. U.S. Department of Health and Human Services, National Institutes of Health. https://www.drugabuse.gov/publications/research-reports/medications-to-treat-opioid-addiction/overview.

5. Miranda A, Taca A. Neuromodulation with percutaneous electrical nerve field stimulation is associated with reduction in signs and symptoms of opioid withdrawal: a multisite, retrospective assessment. Am J Drug Alcohol Abuse. 2017 Mar 16;1-8.
6. Wesson DR, Ling W. The Clinical Opiate Withdrawal Scale (COWS). J Psychoactive Drugs. 2003;35:253-9.
7. Handelsman L, Cochrane KJ, Aronson MJ, Ness R, Rubinstein KJ, Kanof PD. Two new rating scales for opiate withdrawal. Am J Drug Alcohol Abuse. 1987;13(3):293-308. doi: 10.3109/00952998709001515. PMID: 3687892.
8. Beswick T, Best D, Rees S, Bearn J, Gossop M, Strang J. Major disruptions of sleep during treatment of the opiate withdrawal syndrome: differences between methadone and lofexidine detoxification treatments. Addict Biol. 2003 Mar;8(1):49-57. doi: 10.1080/1355621031000069882. Erratum in: Addict Biol. 2003 Sep;8(3):367. PMID: 12745416
9. Huhn AS, Finan PH, Gamaldo CE, Hammond AS, Umbricht A, Bergeria CL, Strain EC, Dunn KE. Suvorexant ameliorated sleep disturbance, opioid withdrawal, and craving during a buprenorphine taper. Sci Transl Med. 2022 Jun 22;14(650):eabn8238. doi: 10.1126/scitranslmed.abn8238. Epub 2022 Jun 22. PMID: 35731889.
10. Yu L, Buysse DJ, Germain A, Moul DE, Stover A, Dodds NE, Johnston KL, Pilkonis PA. Development of short forms from the PROMIS™ sleep disturbance and Sleep-Related Impairment item banks. Behav Sleep Med. 2011 Dec 28;10(1):6-24. doi: 10.1080/15402002.2012.636266. PMID: 22250775
11. Downie WW, Leatham PA, Rhind VM, Wright V, Branco JA, Anderson JA. Studies with pain rating scales. Ann Rheum Dis. 1978 Aug;37(4):378-81. doi: 10.1136/ard.37.4.378. PMID: 686873; PMCID: PMC1000250.
12. Somoza, E., Dyrenforth, S., Goldsmith, J., Mezinskis, J., & Cohen, M., 1995. In search of a universal drug craving scale. Paper presented at the Annual Meeting of the American Psychiatric Association, Miami Florida.
13. McNair, D., Lorr, M., & Droppleman, L. (1971). Manual for the Profile of Mood States. San Diego: Educational and Industrial Testing Service.
14. Form 90-DI Drug Use Assessment (Intake), Center on Alcohol, Substance use, And Addictions (CASAA), University of New Mexico, Albuquerque, NM 87106. http://casaa.unm.edu/inst.html
15. Faul, F., Erdfelder, E., Lang, AG. et al. G*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behavior Research Methods 39, 175–191 (2007). https://doi.org/10.3758/BF03193146
16. Cohen J. (1988). Statistical Power Analysis for the Behavioral Sciences. New York, NY: Routledge Academic

19. REVISION HISTORY

Version Number	Version Date	Summary of Revisions Made
1.0	[redacted]	[redacted]

20.0 APPENDICES

20.1 Appendix I: *Clinical Opiate Withdrawal Scale (COWS)*

Clinical Opiate Withdrawal Scale

For each item, circle the number that best describes the patient's signs or symptom. Rate on just the apparent relationship to opiate withdrawal. For example, if heart rate is increased because the patient was jogging just prior to assessment, the increase pulse rate would not add to the score.

Patient's Name:_____ Date and Time ____/____/____:_____

Reason for this assessment:_____

Resting Pulse Rate: _____beats/minute *Measured after patient is sitting or lying for one minute* 0 pulse rate 80 or below 1 pulse rate 81-100 2 pulse rate 101-120 4 pulse rate greater than 120	**GI Upset:** *over last 1/2 hour* 0 no GI symptoms 1 stomach cramps 2 nausea or loose stool 3 vomiting or diarrhea 5 multiple episodes of diarrhea or vomiting
Sweating: *over past 1/2 hour not accounted for by room temperature or patient activity.* 0 no report of chills or flushing 1 subjective report of chills or flushing 2 flushed or observable moistness on face 3 beads of sweat on brow or face 4 sweat streaming off face	**Tremor** *observation of outstretched hands* 0 no tremor 1 tremor can be felt, but not observed 2 slight tremor observable 4 gross tremor or muscle twitching
Restlessness *Observation during assessment* 0 able to sit still 1 reports difficulty sitting still, but is able to do so 3 frequent shifting or extraneous movements of legs/arms 5 unable to sit still for more than a few seconds	**Yawning** *Observation during assessment* 0 no yawning 1 yawning once or twice during assessment 2 yawning three or more times during assessment 4 yawning several times/minute
Pupil size 0 pupils pinned or normal size for room light 1 pupils possibly larger than normal for room light 2 pupils moderately dilated 5 pupils so dilated that only the rim of the iris is visible	**Anxiety or Irritability** 0 none 1 patient reports increasing irritability or anxiousness 2 patient obviously irritable or anxious 4 patient so irritable or anxious that participation in the assessment is difficult
Bone or Joint aches *If patient was having pain previously, only the additional component attributed to opiates withdrawal is scored* 0 not present 1 mild diffuse discomfort 2 patient reports severe diffuse aching of joints/muscles 4 patient is rubbing joints or muscles and is unable to sit still because of discomfort	**Gooseflesh skin** 0 skin is smooth 3 piloerrection of skin can be felt or hairs standing up on arms 5 prominent piloerrection
Runny nose or tearing *Not accounted for by cold symptoms or allergies* 0 not present 1 nasal stuffiness or unusually moist eyes 2 nose running or tearing 4 nose constantly running or tears streaming down cheeks	Total Score _____ The total score is the sum of all 11 items Initials of person completing assessment: _____

Score: 5-12 = mild, 13-24 = moderate; 25-36 = moderately severe; more than 36 = severe withdrawal

This version may be copied and used clinically.

20.2 Appendix II: *Subjective Opiate Withdrawal Scale (SOWS)*

Subjective Opiate Withdrawal Scale (SOWS)

In the column below in today's date and time, and in the column underneath, write in a number from 0-4 corresponding to how you feel about each symptom RIGHT NOW.
Scale: 0 = not at all 1 = a little 2 = moderately 3 = Quite a bit 4 = extremely

Date

Time

	Symptom	Score	Score	Score	Score	Score	Score
1	I feel anxious						
2	I feel like yawning						
3	I am perspiring						
4	My eyes are teary						
5	My nose is running						
6	I have goosebumps						
7	I am shaking						
8	I have hot flushes						
9	I have cold flushes						
10	My bones and muscles ache						
11	I feel restless						
12	I feel nauseous						
13	I feel like vomiting						
14	My muscles twitch						
15	I have stomach cramps						
16	I feel like using now						
	TOTAL						

Source: Handelsman et al 1987[225]

20.3 Appendix III: [redacted]

[redacted]

[redacted]

20.4 Appendix IV: [redacted]

[redacted]

20.5 Appendix V: [redacted]

[redacted]

[redacted]

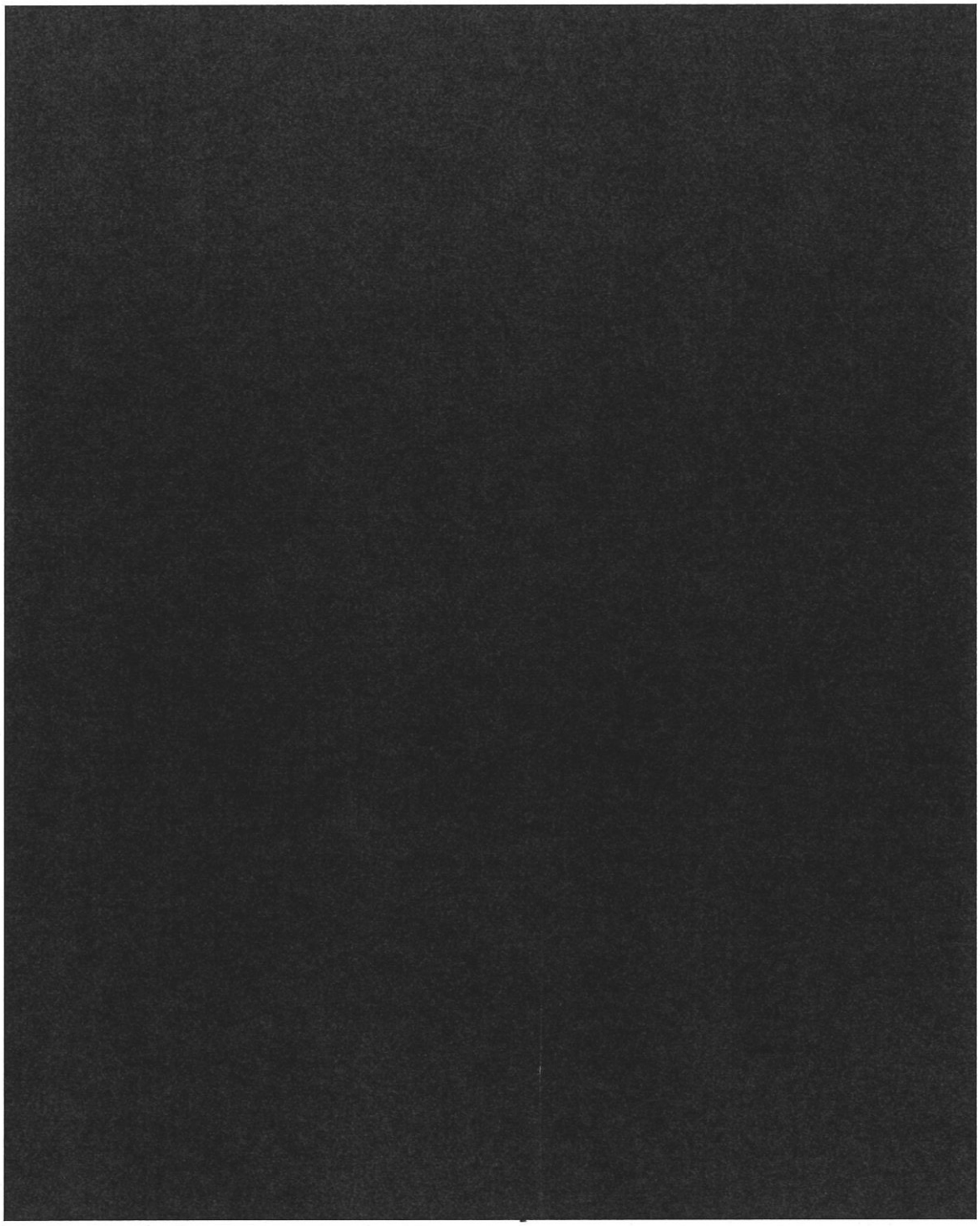
20.6 Appendix VI: [redacted]

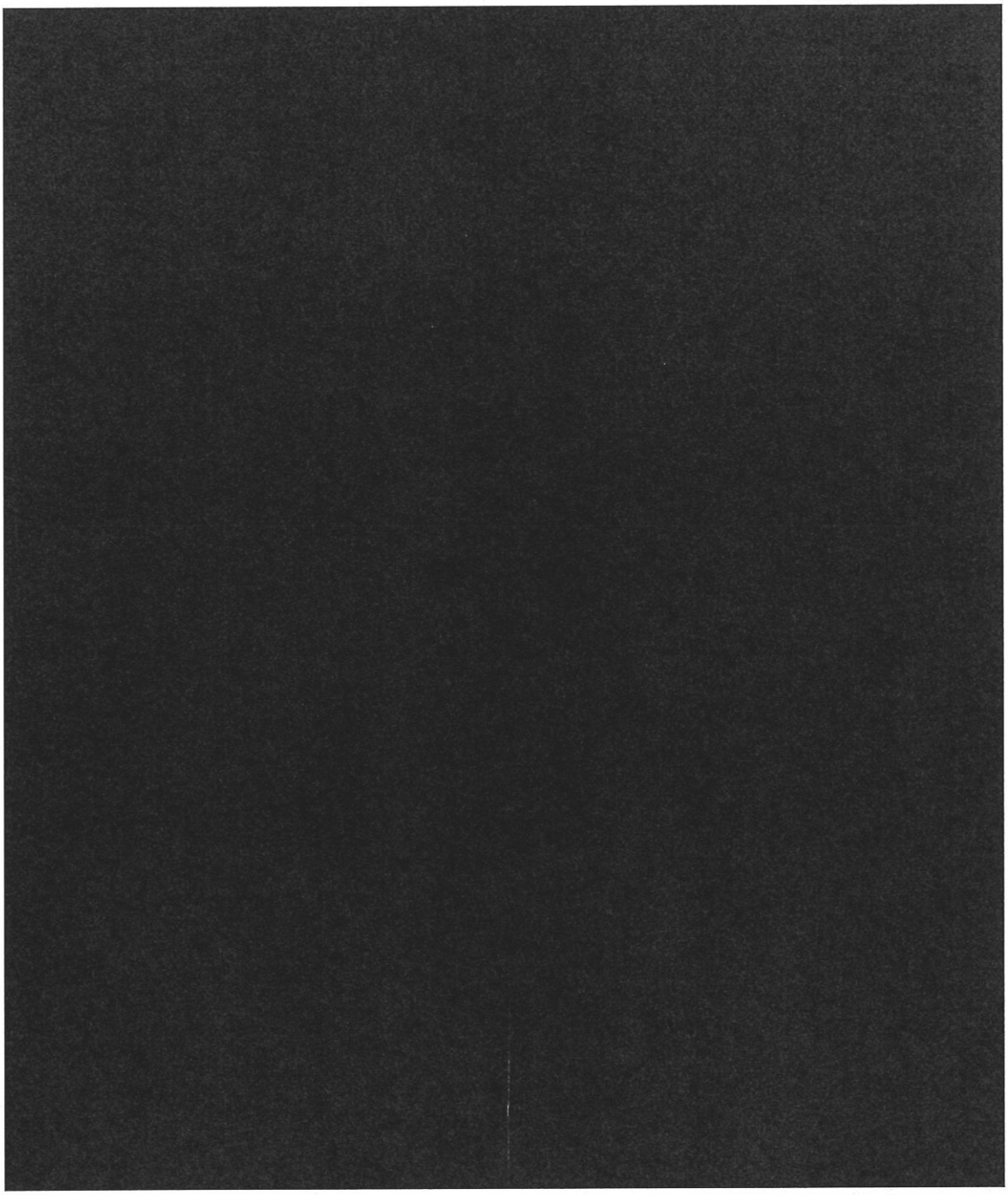
[redacted]

[redacted]

20.7 Appendix VII: [redacted]

[redacted]





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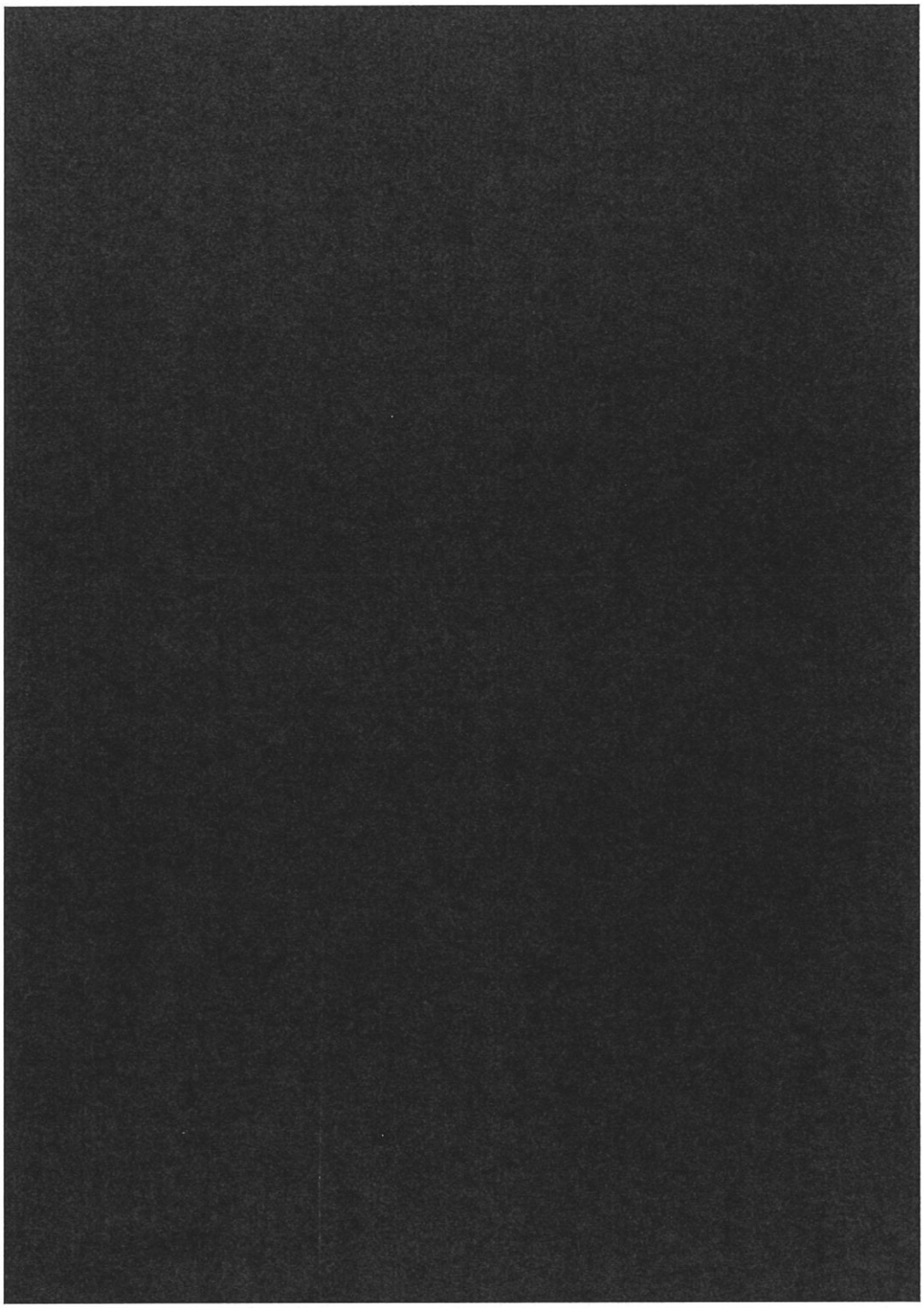

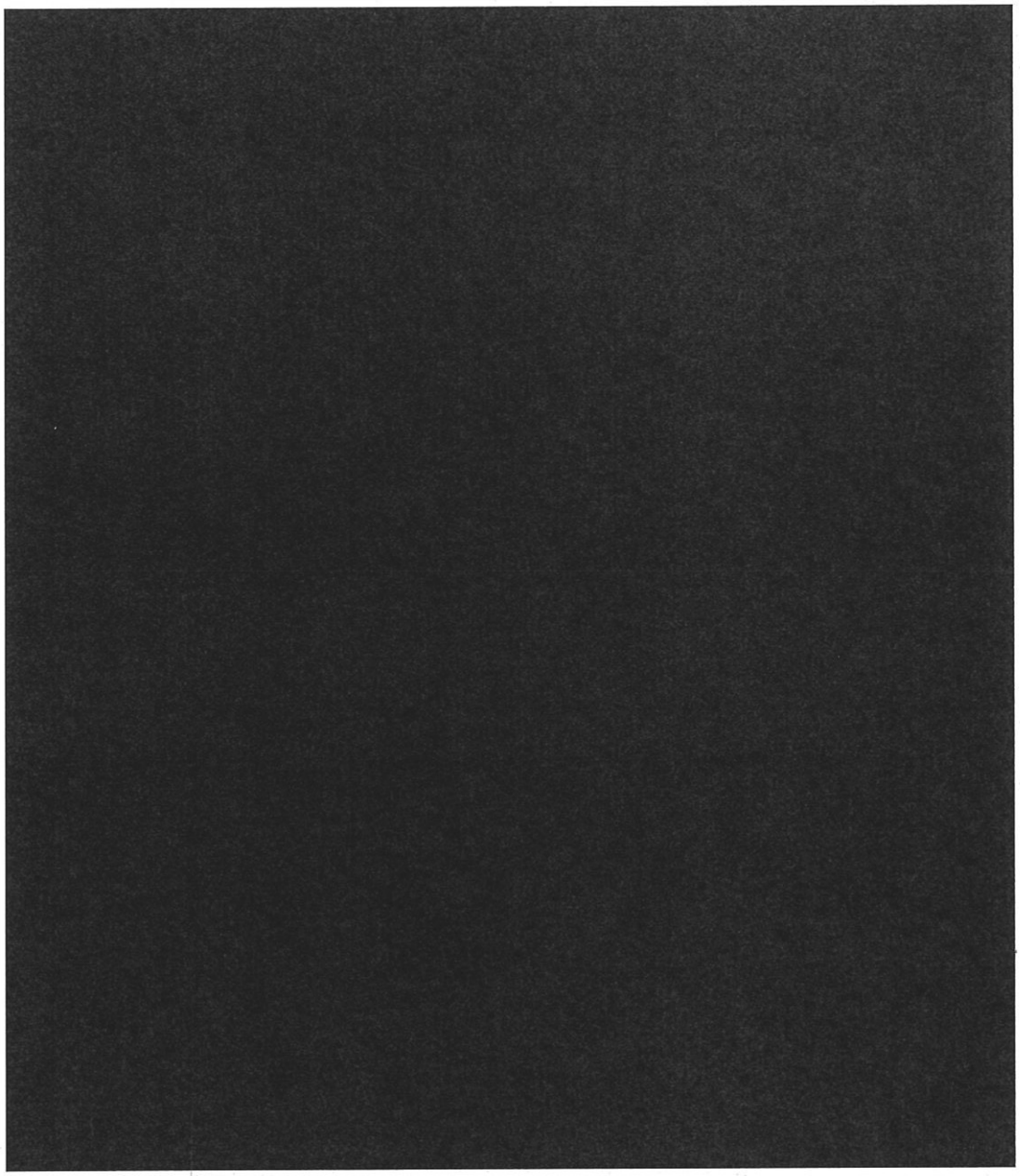

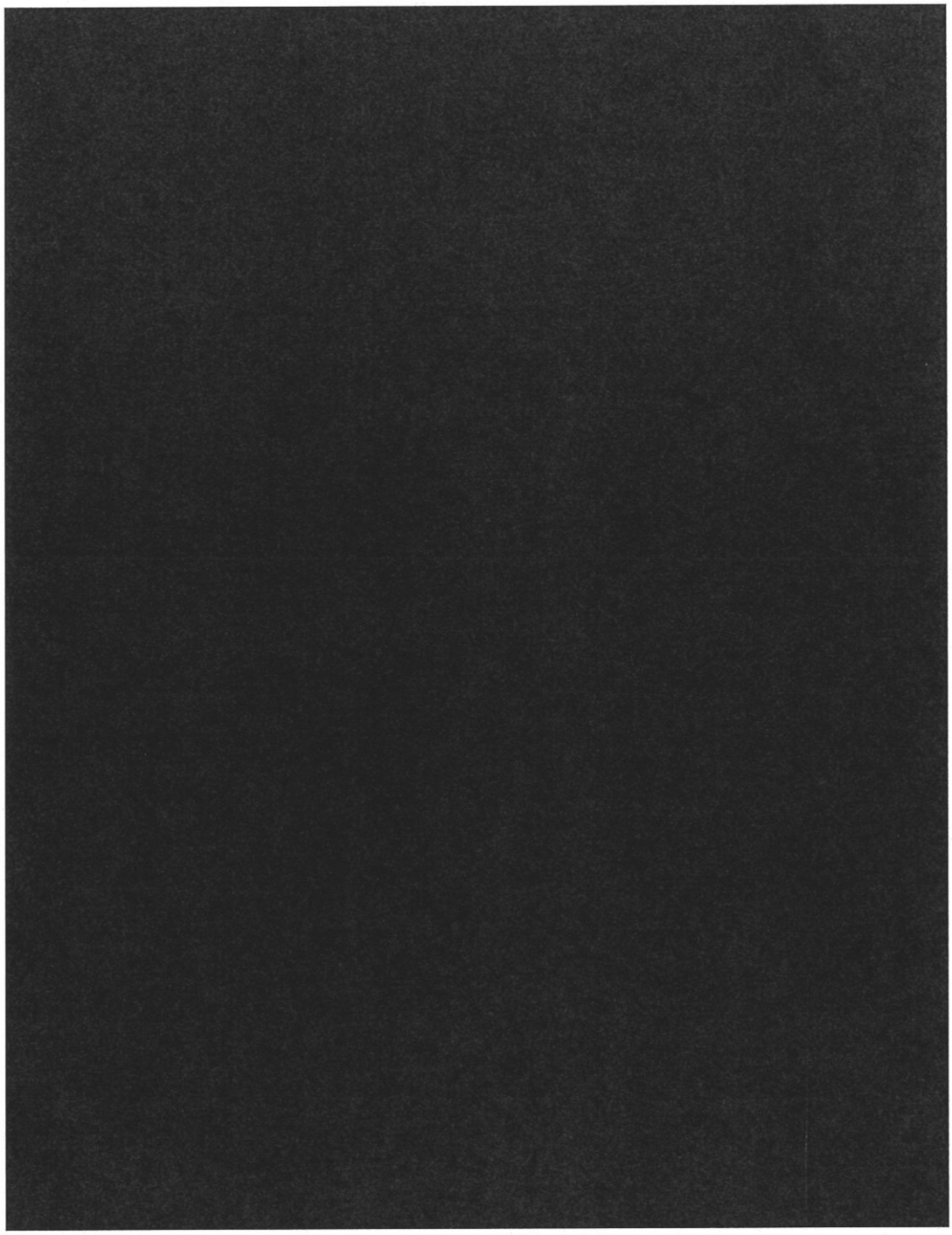

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