WISCONSIN DEPARTMENT OF SAFETY AND PROFESSIONAL SERVICES

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STATE OF WISCONSIN
BEFORE THE MEDICAL EXAMINING BOARD

IN THE MATTER OF THE DISCIPLINARY PROCEEDINGS AGAINST	:	ORDER GRANTING REQUEST FOR BOARD APPROVAL
ELEAZAR KADILE, M.D., RESPONDENT.	:	LS0112061MED

TO:

Attorney Algis Augustine
218 N. Jefferson St. Ste. 202
Chicago, IL 60661

Eleazar Kadile, M.D.
1538 Bellevue St.
Green Bay, WI 54311

On November 21, 2003, the Wisconsin Medical Examining Board ("Board") issued a Final Decision and Order ("Order") limiting Respondent's license to practice medicine and surgery with certain terms and conditions.

On April 15, 2015, the Board considered Respondent's request for prior approval to engage or participate in research on human subjects in order to conduct a research study on topical analgesics. Based upon the information of record, the Board finds and makes the following:

ORDER

1. Respondent's request for approval to engage in research on human subjects is approved as follows. The Respondent requested approval to engage or participate in a specific study under specific terms and conditions. That study, along with accompanying documents submitted by the Respondent to the Board, is attached to this Order. The Board approves the Respondent's participation and/or engagement in this study only so far as the terms and conditions of the study are contained in the attached documents. Any deviation from the terms and conditions of the attached study is not approved by the Board. Should the Respondent wish to deviate from the terms and conditions of the attached study the Respondent shall first petition the Board for approval and receive Board approval before undertaking the deviation. Should the Respondent desire to engage or participate in a specific study, not the subject of the attached study, the Respondent shall first petition the Board for approval and receive Board approval before undertaking another study.

2. This order is effective the date of its signing.

WISCONSIN MEDICAL EXAMINING BOARD

By: Kenneth Simons, MD 4-27-2015

A Member of the Medical Examining Board Date

STATE OF WISCONSIN
BEFORE THE MEDICAL EXAMINING BOARD

ELEAZAR KADILE, M.D., Petitioner.	:	REQUEST FOR PRIOR APPROVAL

NOW COMES ELEAZAR KADILE, MD, by Augustine, Kern and Levens, Ltd., his Illinois attorneys, and moves the Medical Examining Board to grant prior approval to engage or participate in research on human subjects in order to conduct a research study on topical analgesics Study, and as grounds therefor states as follows:

1. Eleazar Kadile is a licensed and registered physician in the State of Wisconsin, license #20408, first granted on October 1, 1976.
2. On November 21, 2003, the Medical Examining Board issued a final decision and order against Dr. Kadile in case number LS0112061MED .
3. As part of the order, in said case, the Medical Examining Board ruled that Dr. Kadile "shall not engage or participate in any research on human subjects without the specific consent of the Board, which consent shall not be unreasonably withheld."
4. Dr. Kadile has been and intends to remain in good standing with the Board since the disciplinary action in 2003.
5. On or about December 23, 2014, Dr. Kadile was approved by Phase 4, LLC, a Delaware limited liability company ("Phase 4"), to be the principal investigator for its "Multi-site investigation of compounded topical medications in pain conditions with variable individual and environmental factors," also known as Study Number 18 ("the Study").

6. As principal investigator, Dr. Kadile is responsible for collecting and maintaining consent forms from all participants at his research site, filling out prescriptions for the product, and submitting all consent forms and pain assessment questionnaires to Phase 4.

7. The Study involves tracking pain assessments from groups of voluntary patients prescribed a topical medication that contains a variety of FDA-approved agents, in hopes that the medication alleviates pain.

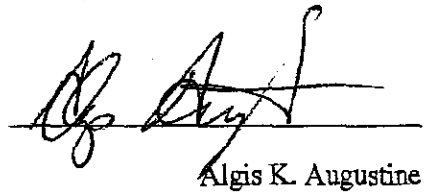
8. Attached to this request are: (1) the agreement between Dr. Kadile and Phase 4; (2) a sample of the monthly pain assessment questionnaire; (3) the authorization to use and disclose personal health information for research form; (4) an informed consent form and authorization to disclose information agreement; (5) and the research plan.

WHEREFORE, ELEAZAR KADILE, M.D prays that the Medical Examining Board grant his request for prior approval to act as principal investigator as aforesaid.

Respectfully submitted,

ELEAZAR KADILE, M.D.,

By: Augustine, Kern and Levens, Ltd., his Illinois attorneys



Algis K. Augustine

This Agreement is entered into by and between:

Phase 4 Research, LLC a Delaware Limited Liability Company, hereinafter called "Phase 4," and Eleazar Kadile, MD, an individual whose principal address is 1538 Bellevue Street, Green Bay, WI 54311, hereinafter called "Principal Investigator." Phase 4 and Principal Investigator may be referred to hereinafter individually as a "Party" or together as the "Parties."

TERMS

1. SCOPE OF WORK

PHASE 4 is carrying out the research ("Study") set forth in Study Number 018 entitled, "Multi-site investigation of compounded topical medications in pain conditions with variable individual and environmental factors," and attached hereto as Exhibit A (as may be amended from time to time) and incorporated herein by reference ("Protocol"), in accordance with this Agreement. Nothing in this Agreement shall be construed as limiting the freedom of PHASE 4 from engaging in similar research with parties other than Principal Investigator.

2. PRINCIPAL INVESTIGATOR

2.1 Principal Investigator is responsible for the direction of the Study at the approved study site, in accordance with the Protocol, applicable PHASE 4 policies, generally accepted standards of good clinical practice, all applicable local, state, and federal laws and regulations governing the performance of clinical investigations.

2.2 Principal Investigator will only conduct the Study at the site approved by Chesapeake Institutional Review Board (IRB) in writing.

3. PERFORMANCE PERIOD

The effective period of this Agreement will be from the date of the last signature of this Agreement and will continue until completion of the obligations established in this Agreement and the Protocol, unless earlier terminated in accordance with Article 14. The effective period may be extended by the mutual written consent of the Parties hereto, as provided in Article 16.

4. RECORDKEEPING; USE OF DATA

4.1 PHASE 4 and Principal Investigator shall prepare and maintain records, reports, and data as provided in the Protocol and in accordance with IRB requirements and all applicable local, state and federal laws and regulations.

4.2 PHASE 4 and Principal Investigator shall cooperate with any regulatory authority with appropriate jurisdiction and allow it reasonable access to relevant Study records and data.

4.3 Principal Investigator shall allow PHASE 4 access to Study records, reports, and data.

5. PAYMENT

5.1 Because of the importance of the Study to the field of medicine and in consideration of the undertakings contemplated herein, PHASE 4 agrees to support the Principal Investigator with financial remuneration, in the amount set forth below:

5.1.1 Principal Investigator will receive one hundred dollars ($100.00) for each "qualified" subject encounter.

5.1.2. A subject encounter is considered "qualified" if;

i. the subject is able to obtain one of the study drugs,

ii. the subject has a diagnosis of a pain condition, and whose medical treatment plan calls for a topical analgesic, AND

ii. the subject is between the ages of 18 and 65.

5.1.3 Subject may not be pregnant or breastfeeding and cannot have government sponsored insurance.

5.1.4 Should a subject not be eligible for the study, that encounter is not considered "qualified" and the Principal Investigator will not be compensated for time with that individual.

5.1.5 Subject encounters may occur no more than once in a thirty (30) day period.

5.1.6 Principal Investigator will receive compensation in the form of a check paid by the fifteenth (15th) day of the month for all qualified subject encounters from the previous calendar month for which at least one month of treatment on a study drug has been completed.

5.1.7 Subject encounters must be recorded and submitted to PHASE 4 in order for Principal Investigator to receive compensation for that encounter.

5.1.8 Principal Investigator will receive an additional one thousand dollars ($1,000.00) once he or she successfully enrolls twenty (20) subjects in the study.

5.2 Checks will be made payable to: "Eleazar Kadile" Checks or accompanying letter will reference Study Number 018 and the Principal Investigator's name, Eleazar Kadile, MD, and will be sent to:

1538 Bellevue Street, Green Bay, WI 54311

6. CONFIDENTIAL INFORMATION

6.1 PHASE 4 does not wish to accept and shall not be obligated to accept any information from Principal Investigator that PHASE 4 considers confidential and shall immediately return to Principal Investigator any such information which it becomes aware it has inadvertently received.

6.2 Principal Investigator has acquired the Protocol from PHASE 4, which, along with all of the research results and data from the Study, is considered the proprietary, confidential and exclusive property of PHASE 4 (collectively, "Confidential Information"). Principal Investigator agrees not to disclose the Confidential Information to any third party without first obtaining the written consent of PHASE 4, which may be withheld at PHASE 4's sole discretion.

6.3 Principal Investigator agrees to limit access to the Confidential Information to those of PHASE 4's employees or agents who have a need to know such information and who have been informed of and are obligated to maintain the confidential nature of such Confidential Information as set forth herein. The Parties shall ensure that Confidential Information will not be used by its directors, officers, employees or agents for any other purpose other than as set forth herein.

6.4 Principal Investigator's obligations of confidentiality will exist during the performance of this Agreement and for five (5) years following termination or expiration of this Agreement, unless disclosure is required by law or regulation. If Principal Investigator is required by law to disclose Confidential Information, it will, sufficiently in advance in order to permit PHASE 4 to take steps to prevent such disclosure, notify PHASE 4 and, prior to any disclosure, consult with and assist PHASE 4 in obtaining a protective order or other appropriate remedy. In any event, the Party disclosing the Confidential Information that is legally required will use best efforts to assure that confidential treatment is accorded any Confidential Information so disclosed.

6.5 The above provisions of confidentiality shall not apply to that part of Confidential Information, which Principal Investigator is able to demonstrate by evidence is/was:

(i) known by Principal Investigator without restriction prior to disclosure under this Agreement and such knowledge can be substantiated by reasonable documentation;

(ii) disclosed to Principal Investigator by a third party without an obligation of confidentiality;

(iii) available to the public through no breach of confidentiality by Principal Investigator; or

(iv) independently developed by Principal Investigator without knowledge or use of Confidential Information disclosed by PHASE 4 under this Agreement.

7. PUBLICATIONS

7.1 PHASE 4 shall be free to publish and present the results and data from the Study, subject to the terms contained below.

7.1.1 The manuscript or abstract proposed to be published or presented shall be submitted to Principal Investigator for review and comment at least thirty (30) days prior to submission for publication or presentation to allow Principal Investigator to protect its rights to any patentable inventions disclosed in such publication or presentation and to permit Principal Investigator to request removal of any confidential information provided by Principal Investigator, if applicable.

7.1.2 Any such publication or presentation shall acknowledge, as appropriate, the contribution of Principal Investigator, its employees, agents and representatives.

8. PATENTS AND INVENTIONS

It is recognized and understood that the existing inventions and technologies of Principal Investigator and PHASE 4 are their separate property, respectively, and are not affected by this Agreement, and neither Party shall have any claims to or rights in such existing inventions and technologies of the other Party.

9. USE OF PHASE 4'S OR PRINCIPAL INVESTIGATOR'S NAME (PUBLICITY)

PHASE 4 and Principal Investigator will obtain prior written permission from each other before using the name, symbols and/or marks of the other in any form of publicity. This shall not include legally required disclosure by PHASE 4 or Principal Investigator that identifies the existence of the Agreement. This paragraph applies to any and all co- and sub-investigators and other Study personnel.

10. NOTICE

Any notice shall be sent to the following addresses. Notice shall be effective on the date of receipt.

PHASE 4: 2884 Walnut Grove Rd, Memphis, TN 38111.

PRINCIPAL INVESTIGATOR: 1538 Bellevue Street, Green Bay, WI 54311

11. INDEMNIFICATION

11.1 Principal Investigator shall indemnify, defend and hold harmless PHASE 4 and its officers, affiliates, agents, representatives, and employees, from and against any and all losses, injuries, harm, liabilities, claims, actions, suits, costs and expenses, including, without limitation, reasonable attorney's fees, for personal injury (including death) or economic loss arising out of the negligence or willful misconduct of Principal Investigator or any other employee or agent of Principal Investigator.

11.2 PHASE 4 shall indemnify, defend and hold harmless Principal Investigator and its officers, affiliates, agents, representatives, and employees, from and against any and all losses, injuries, harm, liabilities, claims, actions, suits, costs and expenses, including, without limitation, reasonable attorney's fees, for personal injury (including death) or economic loss arising out of the negligence or willful misconduct of PHASE 4 or any other employee or agent of PHASE 4.

11.3 PHASE 4 shall promptly notify Principal Investigator of any claim or suit against any party to be indemnified hereunder and shall fully cooperate with Principal Investigator regarding such disposition or settlement.

11.4 Principal Investigator shall promptly notify PHASE 4 of any claim or suit against any party to be indemnified hereunder and shall fully cooperate with PHASE 4 regarding such disposition or settlement.

11.5 Principal Investigator shall not dispose or settle any claim admitting liability on the part of, or impose any obligation on, PHASE 4 or any indemnitee without PHASE 4's prior written consent.

12. INSURANCE

Principal Investigator will maintain during the performance of this Agreement a policy or policies of comprehensive general liability insurance at levels sufficient to support the indemnification obligations in this Agreement. Principal Investigator will provide PHASE 4 with a certificate of insurance evidencing such coverage at the reasonable request of PHASE 4.

13. SUBJECT INJURY

Study subjects will not be reimbursed the cost of obtaining necessary medical treatment for any injuries directly resulting from a Study subject's participation in the Study.

14. TERMINATION

14.1 This Agreement may be terminated by either Party for a material breach of this Agreement by the other Party, which remains uncured after thirty (30) days' prior written notice.

14.2 PHASE 4 may terminate this Agreement for any reason upon thirty (30) days' prior written notice.

14.3 Upon termination of the Agreement, all of Principal Investigator's rights to use the Confidential Information shall immediately terminate.

14.4 Termination of this Agreement by either Party shall not affect the rights and obligations of the Parties accrued prior to the effective date of the termination. Any provision of this Agreement creating obligations extending beyond the term of this Agreement will survive the expiration or termination of this Agreement, regardless of the reason for such termination.

15. APPLICABLE LAW

This Agreement shall be governed by the laws of the State of Tennessee, without regard to its principles of conflict of law. The Parties agree that the provisions of this Agreement are intended to be interpreted and implemented so as to comply with all federal, state and local laws, rules and regulations. If it is determined by any federal, state or local agency, department, or instrumentality that the provisions of this Agreement are not in compliance with laws, rules and regulations applicable to performance under this Agreement, then the Parties agree to modify the provisions and the implementation of this Agreement so as to be in compliance with all applicable federal, state and local laws, rules and regulations as determined by such governmental body.

16. AMENDMENT

This Agreement and the Protocol may only be extended, renewed or otherwise amended by the mutual written consent of the Parties hereto.

17. ENTIRE AGREEMENT

This Agreement, including the Exhibits hereto, represents the entire understanding of the Parties with respect to the subject matter hereof.

18. SEVERABILITY

The invalidity or unenforceability of any term or provision of this Agreement shall not affect the validity or enforceability of any other term or provision hereof.

19. ASSIGNMENT

Neither this Agreement nor the rights or obligations hereunder shall be assignable or otherwise transferred or subcontracted without the other Party's prior written consent.

20. INDEPENDENT CONTRACTOR

In the performances of all services hereunder, Principal Investigator shall be deemed to be and shall be an independent contractor and, as such, shall not be entitled to any benefits applicable to employees of PHASE 4.

21. FORCE MAJEURE

Neither Party shall be liable for any failure to perform as required by this Agreement to the extent such failure to perform is due to circumstances reasonably beyond such Party's control, including, without limitation, labor disturbances or labor disputes of any kind, accident, failure of any governmental approval required for full performance, civil disorders or commotions, acts of aggression, acts of God, energy or other conservation measures imposed by law or regulation, explosions, failure of utilities, mechanical breakdowns, material shortages, disease, or other such occurrence.

22. DEBARMENT

22.1 Principal Investigator will not use in any capacity, in connection with the Study, the services of any individual, corporation, partnership or association which:

(i) is debarred under 21 U.S.C. 335a; or

(ii) is disqualified as a clinical investigator under the provision of 21 C.F.R. 312.70.

22.2 In the event that Principal Investigator becomes aware of the debarment or disqualification of any such individual, corporation, partnership, or association providing services under this Agreement, Principal Investigator shall promptly notify PHASE 4.

23. COUNTERPARTS

This Agreement may be executed in any number of counterparts, which when taken together, will constitute one original, and photocopy, facsimile, electronic or other copies shall have the same effect for all purposes as an ink-signed original. Each Party consents to be bound by pdf, photocopy or facsimile signatures of such Party's representative.

24. NO WARRANTIES

PHASE 4 MAKES NO WARRANTIES, EXPRESS OR IMPLIED, CONCERNING ANY MATTER WHATSOEVER, INCLUDING WITHOUT LIMITATION, THE DATA AND RESULTS OF THIS STUDY OR THE OWNERSHIP, MERCHANTABILITY, OR FITNESS FOR A PARTICULAR PURPOSE OF SUCH DATA AND RESULTS.

IN WITNESS WHEREOF, the Parties hereto have executed authorized.

PRINCIPAL INVESTIGATOR:

By: _____ (Signature)

Name: Eleazar Kadile, MD

Title: _____

Date: _____

PHASE 4:

By: _____ (Signature)

Name: _____

Title: _____

Date: _____

EXHIBIT A: PROTOCOL

Monthly Pain Assessment Questionnaire

Patient's ID: _____ Date: _____

Study Medication Received: _____ Average # Pumps/Day: _____

Other pain medications (name, strength, and frequency of use):

_____

	None	Mild	Moderate	Severe
Throbbing				
Shooting				
Stabbing				
Sharp				
Cramping				
Gnawing				
Hot/Burning				
Aching				
Heavy				
Tender				
Splitting				
Tiring/Exhausting				
Sickening				
Fearful				
Punishing/Cruel				

No Pain |———————————————————| Worst Possible

Assessment of Neuropathic and Nociceptive Pain Characteristics
(Adapted from the LANSS and DN4 Questionnaires)

Patient's ID: _____ Date: _____

Sex: _____ Age: _____ Race: _____ Height: _____ Weight: _____

Pain condition: _____ Body Area: _____

1. Does your pain feel like strange, unpleasant sensations in your skin? (Words like pricking, tingling, pins and needles might describe these sensations). □ YES □ NO

   If yes, check which if any apply: □ tingling □ pins and needles □ numbness □ itching

2. Does your pain make the skin in the painful area look different from normal? (Words like mottled or looking more red or pink might describe the appearance). □ YES □ NO

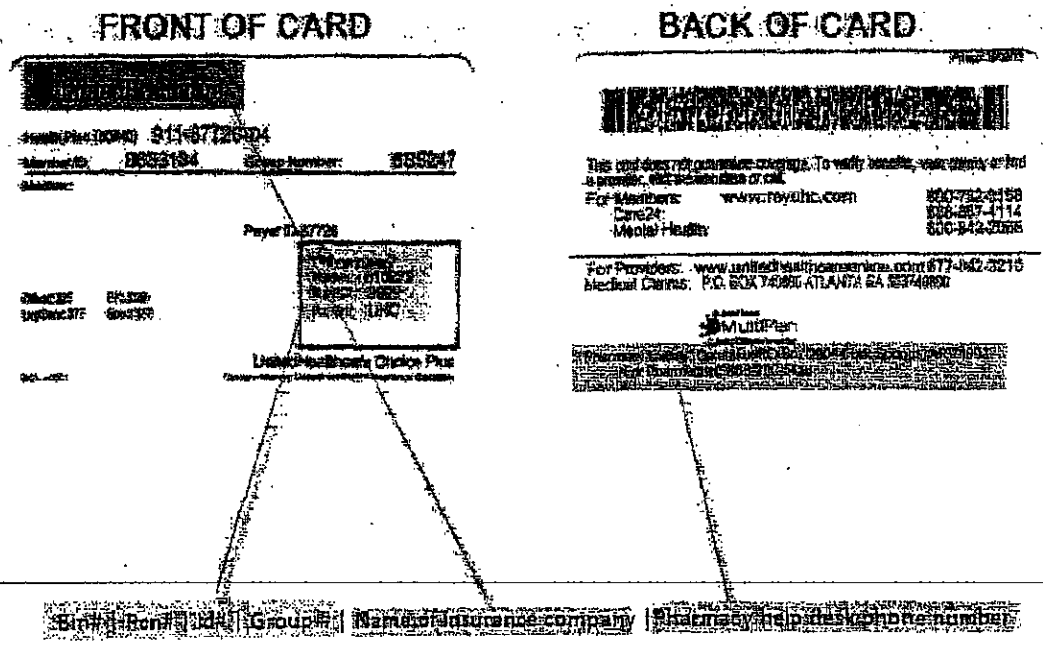
3. Does your pain make the affected skin abnormally sensitive to touch? (Getting unpleasant sensations when lightly stroking the skin, or getting pain when wearing tight clothes might describe the abnormal sensitivity). □ YES □ NO

4. Does your pain come on suddenly and in bursts for no apparent reason when you're still? (Words like electric shocks, jumping and bursting describe these sensations). □ YES □ NO

5. Does your pain feel as if the skin temperature in the painful area has changed abnormally? (Words like hot and burning describe these sensations). □ YES □ NO

   If yes, check which if any apply: □ burning □ painful cold

Insurance Reimbursement Cheat Sheet



Pharmacy benefit cards are provided to patients often as separate cards from their standard health insurance cards. The image above demonstrates the information a pharmacist requires to process a claim for a prescription medication. BIN, PCN, ID, GROUP, Name of Insurance Company, and Pharmacy help desk phone number in case of an issue with processing. Gathering this information from the patient will ensure the process will proceed as smoothly as possible and the patient will receive their medication expediently.

Authorization to Use and Disclose Personal Health Information for Research
This section explains who will use and share your study-related health information if you agree to be in this study. You do not have to sign this form to allow the use and sharing of your protected health information; however, if you do not sign this form, you cannot participate in the study.

During the study, your healthcare provider will maintain your medical records ("medical records") according to their own record retention policy. Healthcare providers will assign a unique number to each participant that does not relate to subject identifiers. The questionnaires ("study information") do not contain information that will allow the individuals who collect the data to identify the participants. No identifiers to participants will be collected or made available to those collecting your study information.

The individuals who are gathering the data will not be able to access the pharmacy's records, both electronically and physically. The computers used by those gathering the data will not have access to pharmacy records, nor will those individuals have access to any physical copies of protected health information.

The pharmacy staff, including but not limited to the pharmacists and pharmacy technicians will not have knowledge of which subjects are participants in the study.

If you sign this form:

- You allow the study healthcare provider and study staff to use your records to carry out this study.
- You allow the study healthcare provider and/or study staff to share your "study information" with the sponsor, people who work with or for the sponsor, and other researchers and staff involved in this study.
- You allow the study healthcare provider or sponsor to use some of the facts about your being in the study in books, magazines, journals, and scientific conferences. If this happens, only your "study information" will be used. No identifying data will be used.
- You allow the study healthcare provider to share your "medical records" and this signed consent form with government agencies, including the U.S. Food and Drug Administration (FDA) and other government agencies in the U.S. and other countries. The study healthcare professional may also share your "medical records" with ethics committees, like an Independent Review Board (IRB). These agencies may use your records to check the study information, how researchers are doing the study, participants' safety, and the results of the study.

- You allow the study healthcare professional to share your "medical records" with your health care payer to resolve your claim if you are hurt because of being in this study. If this happens, the study healthcare professional or the sponsor may share your records with their insurance carriers to resolve your insurance claim.

There are national and state laws that make the study healthcare professional and/or study staff protect the privacy of your records. The study medications are provided by licensed compounding pharmacies that are governed by federal and state laws concerning confidentiality of private health information. Your records will be maintained in the same confidential and secure manner that all other pharmacy records are kept.

If you would like to know more about how the sponsor will protect the privacy of your records, ask the study healthcare provider how to get this information.

You have the right to see and copy your "study information." However, if you sign this form, you might not be able to see or copy some of your "study information" until after all participants finish the study.

Even if you leave the study early, the study healthcare provider and study staff will still be able to use and share your "study information" as described above unless you cancel your consent to use and share your "study information."

You can cancel your consent to use and share your "study information" at any time. If you want to cancel your consent to use and share your "study information," you must write a letter to the study healthcare provider at the address listed on page 1 of the consent form. If you cancel your consent:

- You will not be able to be in the study
- The study healthcare provider will not be able to use or share your "study information" or "medical records" unless it is necessary to protect the integrity of the study.

YOUR AUTHORIZATION TO USE AND SHARE YOUR RECORDS EXPIRES IN 50 YEARS. If you do not cancel this consent form within 50 years, then the study healthcare provider and the study staff will be able to use and share your records for up to 50 years.

You will receive a signed and dated copy of this form for your records.

_____

Signature of subject Date

INFORMED CONSENT FORM
AND
AUTHORIZATION TO DISCLOSE HEALTH INFORMATION

Study Title:	**Multi-site investigation of compounded topical medications in pain conditions with variable individual and environmental factors**
S Number:	**018**
Sponsor:	**Phase 4 Research, LLC**
Principal Investigator:	**Eleazar M. Kadile, M.D.**
Telephone:	**(262) 395-4435 (24 Hours)**
Address:	**Center for Integrative Medicine** **1538 Bellevue Street** **Green Bay, WI 54311**

You are being asked to take part in a research study. As a participant in this study, you will be asked to keep a record of your current pain management treatment. Your healthcare provider will also keep a record of your current pain management treatment. Your current pain management treatment will not be affected by participation. Likewise, your current pain management treatment will not be affected if you choose not to participate.

As a possible participant in a research study, you should have this Informed Consent Form (ICF) presented to you. No procedures will be conducted before you read and sign this ICF. If you live in California, you should have already received the California Experimental Subject's Bill of Rights.

This consent form describes the purpose, procedures, and possible benefits and risks of the study. This form will also explain how your medical information will be used and who may see it. Once you have been fully informed about the study in terms you can understand and have had your questions answered, you will be asked to sign and date this form. In signing this form you indicate that you wish to take part in the study and to allow your medical information to be collected, used, and shared with certain persons involved in the study. If you do not sign and date this form, you may not take part in the study. You will be provided with a copy of this consent form after signing.

Your participation in this study is completely voluntary. You do not have to participate in this study. You may decide not to participate or you may quit the study at any time without penalty and without affecting your medical care.

Your healthcare provider is paid by the Sponsor (Phase 4 Research, LLC) to conduct this study. Your healthcare provider will not alter your course of pain management treatment based on your participation in this study.

Purposes of the research

The purpose of the study is to examine the long and short-term effects of topical pain creams. The study is being conducted nationwide. The pain creams being studied are compounded medications. This means that they are available by prescription only and are made only when a licensed compounding pharmacy receives a valid prescription from a healthcare provider. In other words, it is made specifically for each subject.

Study Visits / Procedures

Participants will be required to fill out a pain assessment questionnaire each day. This should not take more than one (1) minute. The questionnaire will be provided once you have agreed to become a participant in this study. Your healthcare provider will collect questionnaires at each regularly scheduled office visit. You do not need to schedule additional appointments based on your participation in this study. The study will continue during the course of your current pain management treatment. Once your use of a study pain cream stops, so does your participation in the study. Participation will not last longer than 2 years, although your healthcare provider may continue to prescribe you the study pain cream if it is still in your plan of your current pain management treatment.

At each office visit, your healthcare professional will ask you a series of questions, similar to the pain assessment questionnaire you will fill out at home.

Possible Side Effects and Risks of the Study Drug

Although allergies to any of the medications in the pain cream formulas are rare, please discontinue use and call your healthcare provider if any of the following should occur: rash, hives, itching, swelling of the application area, redness, or irritation of the application area. Sometimes a little tingling in the area of application will occur. This is normal. If the tingling lasts longer than sixty (60) minutes or turns into itching, please discontinue use and call your healthcare provider.

There is also the possibility that you could experience other side effects that are still unknown at this time and that are unforeseeable. If any new information is learned during this study that may influence your decision to continue being in the study, the study healthcare provider will tell you about this new information.

In all cases, a study staff member will be available at all times to answer your questions about the study and how you are feeling during the study. The study healthcare provider may also stop your participation in the study due to side effects or if he feels it is in your best interest even if you wish to continue in the study.

Potential Benefits and Alternatives to Participation

There are numerous, known benefits of using the study pain creams. Some benefits include: reduced use of oral opioids and treating localized pain. However, since you will be prescribed the compounded pain cream whether you participate in this study or not, there is no expected benefit to you from taking part in this study.

Please talk with your healthcare provider if you have any questions or concerns. The alternative to participation is to continue your prescribed course of pain management treatment and not complete the pain assessment questionnaires.

Study Staff Payment

Phase 4 Research, LLC, is paying the study healthcare providers/principal investigators for their work in this study.

Costs / Financial Compensation

In order for you to take part in this study, you must have the ability to pay for the study drug, either through insurance or cash.

You will receive a total of $50.00 for each month you are in the study. If you do not finish the whole month, you will still receive $50.00 for the partially completed month. Your healthcare provider or study staff can tell you more about when you will receive compensation.

Treatment for Injury

If you have any questions or concerns, please contact either your healthcare provider or the pharmacy that dispensed the study pain cream. If it is an emergency, go to the nearest emergency room or call 911.

Since the use of the study cream is part of your usual pain management treatment, the Study sponsor will not reimburse you for any costs associated with injury resulting from the use of the study pain cream. The Study sponsor will also not be liable for any incidental or consequential damages.

You still have the right to make a claim through the legal system even if you sign this form, accept medical care, or accept payment for medical expenses.

Confidentiality

Your current healthcare provider will keep your medical records confidential pursuant to state and federal laws. Your participation will not change the way your medical records are kept by your healthcare professional. You will be given a random identification code that has no relation to any of your confidential medical information.

The only person or entity that has access to your medical records is your healthcare provider. The study will only identify you by a random identification code that is assigned to you by your healthcare provider.

All pain assessment questionnaires and other participant data will be identified only by the random identification code. No other entity will have access to your medical records besides your healthcare provider and the pharmacy filling your medication order.

As an added level of privacy, your pain assessment questionnaires will be stored in a locked cabinet with restricted access.

While participating in this study, Phase 4 Research, LLC, an Independent Review Board (IRB), and various federal agencies (such as the Food and Drug Administration [FDA] or similar agencies of other countries) will need to have access to your study records. Your study records only include your pain assessment questionnaires which have no personally identifying information.

By signing this form, you are giving them your permission to allow people who work within these organizations to view your study records. This does not authorize them to view your medical records.

Voluntary participation

Your participation in this study is completely voluntary. You may decide not to participate or you may withdraw from the study at any time without penalty and without affecting your medical care. In addition, the study healthcare provider, Sponsor, or IRB may end your participation at any time without your consent if you no longer meet the requirements for the study, if there is a safety concern, or if you do not follow the directions for the study that have been outlined in this consent form.

Legal Rights

You will not lose any of your legal rights by signing this consent form.

Questions

You can ask questions about this consent form or the study (before you decide to start the study or at any time during the study). Questions may include:

- Who to contact in the case of a research-related injury or illness.
- Any payment for being in the study.
- Your rights and your responsibilities as a study subject.
- Other questions.

Contact the study healthcare provider or their designated study staff with any questions or concerns. Their telephone number is printed on the first page of this form. If you have any questions or complaints about your rights as a research subject, contact:

- By mail: Study Subject Adviser
  Chesapeake IRB
  6940 Columbia Gateway Drive, Suite 110
  Columbia, MD 21046
- or call toll free: 877-992-4724
- or by email: adviser@chesapeakeirb.com

Please reference the following number when contacting the Study Subject Adviser: Pro00010658.

An IRB is a group of people who review research studies to protect the rights and welfare of research participants.

By signing this consent for you agree that you have had the opportunity to read the informed consent form thoroughly and had the opportunity to ask questions about this study and you have, to your satisfaction, received answers to those questions.

You will receive a copy of this signed and dated consent form.

Signatures

_____
Printed name of Subject

_____
Signature of subject Date

_____
Printed name of person presenting consent

_____
Signature of person presenting consent Date

_____
Printed name of Witness

_____
Signature of Witness Date

_____
Subject ID

Daily Pain Journal

Patient's ID: _____ Date: _____

Number of pumps required to achieve desired result: _____

Number of times medication was applied today: _____

Other pain medications (name, strength, and frequency of use):

_____

Present Pain Intensity:
(circle one below)

0 No Pain
1 Mild
2 Discomforting
3 Distressing
4 Horrible
5 Excruciating

No Pain ——— Worst Possible

Principal Investigator
Instruction Sheet for Study No. 018:

Multi-site investigation of compounded topical medications in pain conditions with variable individual and environmental factors (Referred to as "Topical Analgesics Study")

December, 2014

This document will serve as the Standard Operating Procedure for principal investigators involved in the study, and will provide answers to commonly asked questions.

1. **Conducting the Informed Consent Process.**

   a. Investigators are responsible for informing potential research subjects of the nature of the study, the risks and benefits thereof, the alternatives to participation, and all other information necessary for the subjects to make an informed decision of whether or not to participate.
   b. The PI or trained site staff will conduct the consent process in a private room. The person conducting the consent discussion will discuss the study and be available for any questions.
   c. The individual conducting the consent process is responsible for assessing that the subject understands the information provided and gives voluntary consent, free of coercion or undue influence.
   d. Consent forms will be signed and dated by both the subject and the person conducting the consent discussion.
   e. A signed and dated copy will be provided to the subjects.
   f. All consent forms will be collected and maintained by the Principal Investigator at each site.

2. **Submitting Prescriptions**

   a. Although your patients may utilize any compounding pharmacy, you will be provided with a customized prescription pad.
      → The pad will have the pharmacy's fax number on the top.
      → To use a different compounding pharmacy, please contact us for pharmacy approval.
   b. Fill out the pertinent patient information.
   c. Fax the signed and dated prescription to an approved compounding pharmacy of your choice.

3. **Submit the signed informed consent forms and pain assessment questionnaires to Phase 4**

   a. Informed consent forms and pain assessment questionnaires may be submitted in the following ways:
      i. Scanned and emailed to:
         info@phasefourresearch.com
      ii. Faxed to:
         (901) 881-3409
         Attention: Study 018
      iii. Mailed to:
         Phase 4 Research, LLC
         2884 Walnut Grove Rd
         Memphis, TN 38111

4. **Obtain Compensation for Patients and PI's**

   a. Principal investigators who utilize pre-approved pharmacies will receive compensation in the form of a check paid by the fifteenth (15th) day of the month for all qualified subject encounters from the previous calendar month for which at least one month of treatment on a study drug has been completed.
   b. Principal investigators who utilize non-approved pharmacies will receive compensation after Phase 4, the non-approved pharmacy, and the principal investigator reconcile records.
   c. Principal investigators will be mailed Visa gift cards as compensation to be given to each patient involved in the study. These will be dispersed in the practice to these patients once per month.

Commonly Asked Questions

1. Is this a double blind, controlled study?

   No, this is purely an outcome assessment study. It is more akin to a Phase IV study. We are not manipulating any aspect of patient care, only observing outcomes. We will analyze the efficacy of compounded topical analgesic creams in various pain conditions and in relation to a variety of other clinical and demographic variables.

2. Are the patients compensated?

   Yes, the patients are compensated $50 per month in which they are enrolled in the study.

3. Do the patients get the medication for free?

   Yes and no. The patient must obtain the study medication and have their private insurance pay for it. Depending on their insurance plan, they may be required to pay a copay to obtain the medication.

4. For how long can the patients participate in the study?

   Up to five years or until they no longer need the medication.

5. On average, how many times will I see a patient for this study?

Subject encounters, for the purposes of the study, may occur no more than once in a 30 day period.

6. How are principal investigators compensated?

- Principal investigators receive $100 per qualified subject encounter.
- Subjects who are unable to obtain the study drug are not considered "qualified" and no compensation will be received for that encounter.
- It is anticipated that approximately half of the patients will not have their insurance pay for the drug.
- Phase 4 will send checks at the end of the month in relation to the number of "qualified" subject encounters, as compensation for the PI's time in carrying out the duties detailed in this document and the approved protocol.
- Pain assessment questionnaires must be received by Phase 4 in order for the physician to be compensated for each encounter.

7. What are the study medications?

We are primarily investigating five commonly formulated topical medications based on our research of compounding practices in the US. These formulas provide good private insurance coverage for patients. They are listed on the prescription pad provided to each participating study site, as well as the approved protocol. Physicians are able to make modifications to these formulas based on their patients' needs and their medical expertise. These modifications should be listed on the patient's monthly pain questionnaire so that the outcome data may be treated appropriately.

8. Are these compounded formulas FDA approved?

Compounded medications are not FDA approved as they are custom medications made to order and not mass-produced on the scale seen with bulk-packaged pharmaceutical products. The compounded medications in this study do however incorporate all FDA-approved ingredients that were produced in manufacturing facilities with the highest quality controls and periodic FDA oversight much like commercially available pharmaceuticals.

9. What is the expected duration of the study?

The study has been designed to last five years, during which data analysis and reports will be instrumental in designing follow-up studies and disseminating what we have learned in the form of papers and presentations.

10. How does this study impact my medical practice?

- Treat your patients in the same manner you would in your normal practice.
- Either you or a designated staff member(s) you supervise will provide the patient with an informed consent form that will be provided to you and answer any questions the patient may have.
- You or designated staff member(s) will go over an in-office pain assessment questionnaire.
    - This questionnaire is composed of items derived from established standardized pain surveys as explained in the approved protocol.
- This process can be done while the patient is in the exam room waiting to be seen for instance.

11. What do the patients have to do?

- We ask that the patients fill out daily pain assessment questionnaires describing:
    - How many times they applied the drug that day,
    - How many pumps of the medication they used each time,
    - What other pain relievers they used that day, and
    - What their level of pain was for that day.
- Return the daily pain assessment questionnaires to your office during the next scheduled visit for submission. (An online portal is being designed for patients to anonymously upload this information on their own).
- This daily questionnaire is not absolutely mandatory as we know it is impossible to enforce daily compliance, but patients should be encouraged to gather these data as it will improve the resolution of our analyses and patients as well as doctors will eventually be able to view their progress online.

12. Can any pharmacy fill my patients' prescriptions?

- Yes, any pharmacy can fill your patients' prescriptions. We currently have 4 approved pharmacies. In order to clear additional pharmacies for inclusion in the study, you must contact us and submit a simple request to do so. We will then contact the pharmacy and introduce the study's compounding protocols and standards of quality for the ingredients included in the compounds used for this study. In this way we will ensure standardization of treatments. Inspections will be required as in our other participating pharmacies to ensure that these standards are upheld.

13. What are the inclusionary criteria?

- Any patient that you feel would benefit from using a topical analgesic
- Between the ages of 18-65
- Not pregnant or breastfeeding
- Access to and ability to pay for study drugs.

14. Where do the subject encounters take place?

Encounters can only occur at the study site (clinic) approved by the IRB.

RESEARCH PLAN

Study Number: 018
Sponsor Name: Phase 4 Research, LLC
PI: Multi-site investigation
Study Title: Multi-site investigation of compounded topical medications in pain conditions with variable individual and environmental factors
IRB No.:
Date: October 21, 2014

1. Aims/objectives/research question/hypotheses:

Physiological conditions that lead to pathological or heightened pain perception are often cited as factors that most detrimentally affect the quality of life for patients. Research into the efficacy of approved and currently available analgesics becomes increasing complex given the many etiologies of pain. In the proposed studies, we seek to assess the long-term efficacy of a compounded topical medications containing a variety of FDA-approved agents (e.g., ketamine, gabapentin, flurbiprofen, topiramate), examining a wide range of demographics and variables that have been suggested to influence treatment efficacy. These include variables that are both known to affect skin absorption properties (e.g., environmental factors such as humidity and temperature) as well as variables that have yet to be assessed (e.g., skin surface or musculoskeletal area receiving treatment). Following groups of patients who are currently or newly prescribed a given topical compound, we will record changes on various commonly used scales for pain assessment. This will be conducted by proxy through participants' own healthcare providers who will provide an estimation of the patient's current pain state as well as changes over the duration of the experiment. As we are not influencing the participants' normal course of treatment or providing a controlled, placebo condition, our primary objective is to perform an observational study to gather preliminary information regarding the use of the topical compounds among a wide range of demographics and their rate of prescription/use for various muscle/skin areas. These results will be compared to other compounded pain formulations containing commonly prescribed analgesic agents. Furthermore, these results will be disseminated to the medical community to increase awareness and understanding of the factors that impact the efficacy of topical pain management.

2. Background and rationale:

Pain is defined as a multidimensional entity involving nociception, transduction of peripheral stimuli to the central nervous system, modulatory activities, affective responses, as well as behavioral effects, according to the International Association for the Study of Pain[1]. Despite considerable technological advances in the study of mechanisms of pain and the development of an array of treatments, chronic pain remains a challenge to healthcare providers and those afflicted. With continued understanding of the complexity of the pathophysiology of pain, new routes of administration have been explored, balancing the drug efficacy with the minimization of undesirable systemic effects[2].

Patients often suffer with continued troubling nociceptive activity throughout the musculoskeletal and skin surfaces following treatments with typical medications such the nonsteroidal anti-inflammatory drugs (NSAIDs), capsaicin, and lidocaine. Many treatment regimens rely on the use of systemically-administered medications. Topical administration (as used in compounded creams and lotions) offers the benefits of depositing medications within localized outer layers of the skin, minimizing systemic absorption and unwanted central nervous system effects[3,4].

To date many pharmaceutical agents from a diverse range of drug classes have been used in the preparation of topical analgesics. Numerous studies have examined the efficacy and safety of transdermal drug delivery in pain management, proposing that local analgesic effects arise through activity at a variety of peripheral receptors, including opioid receptors and calcium and sodium channels[5-7]. Furthermore, the majority of these studies (as in the case of ketamine) have relied on transdermal (i.e., cutaneously applied patches) forms. Thus, assessing the efficacy of many commonly used analgesic agents in gel or ointment form and their role in topical pain treatment remains a strong target for further investigation.

We hope to comparatively assess efficacy among several widely prescribed compounding agents. These may include but are not limited to flurbiprofen, lidocaine, topiramate, tramadol, and cyclobenzaprine [see attached list of possible analgesic cream formulations]. As we are not manipulating or influencing the diagnosis or recommendations of healthcare providers, the combinations and dosages of these compounds are not known *a priori*. Nevertheless, we believe these data to represent meaningful information for efficacy comparisons.

Beyond physiological mechanisms of pharmacological agents, adequate skin permeation is central to the efficacy of topical analgesics. A variety of adjuvants such as permeation enhancers, emollients, and preservatives are added to active agents in order to control drug concentration, increase absorption, maintain the drugs at the targeted site, and thus increase analgesic activity[2]. In all cases, the penetration of the topical drug is limited by the stratum corneum – the outer layer of the keratinocytes that shields the living epidermal layers. Below these layers, a variety of mechanoreceptors and nociceptors of diverse structure and function transduce tactile and nociceptive signal. Animal models have indicated that variability in transdermal absorption rate arises from the topical agents' ability to navigate through the superficial skin layers[8,9]. The influence of skin and its barrier functions are often described through transepidermal water loss (TEWL) measurements, and these are measurements are known to be effected by environmental (temperature and humidity) or individual-related factors[10-12]. Age and sex-related studies of TEWL have showed mixed results, with older males sometimes showing decreased water loss[13-15]. Similarly, studies of water permeation through the skin of people of differing races have drawn varying conclusions, ranging from increased TEWL in the skin of African American populations[16] to there being no significant difference[17,18]. Anatomical site of the skin is known to contribute to TEWL, with greatest permeability in the hands and feet[19,20] and least in the abdomen and back[20,21]. Furthermore, a variety of environmental conditions have shown to affect skin-related water loss and permeability. These include ambient air temperature[22,23], ambient air humidity[24-26], seasonal variation[27], and geographical variation (as a reflection of several of these environmental variables). In examining a wide variety of these individual and environmental variables in patients with pain conditions, we seek to develop a broad dataset reflecting the efficacy of commonly-prescribed topical analgesic compounds to be used in the design of more targeted studies and experimental approaches.

3. **Participants**:

In order to minimize any possible risks to participants, study participants will be selected by their current healthcare providers. The enrollment period is for five (5) years. Each participant's involvement in the study will not last longer than 2 years, although their healthcare provider may continue to prescribe the studied pain cream if it is still in their plan of treatment.

Inclusion:

- 18 and 65 years of age
- Diagnosis of a pain condition
- Access to and ability to pay for study drugs, either through insurance or cash.

- Already being treated with or already has a plan to be treated with a topical pain formulation

Exclusion:

- Participants who are unwilling or unable to obtain the active pharmaceutical ingredients proposed in the form of a topical medication.
- Participants whose insurance is provided in whole or in part by any government healthcare program
- Pregnant and nursing women
- Participants who do not comprehend the English language sufficiently to consent to be involved in the study or to accurately respond to the study questionnaires.

Patients will be invited to participate based on the recommendation of their healthcare provider. Participants will be included if, upon the healthcare providers' evaluation, they are prescribed one of several compounded creams as part of their routine treatment. Examples of possible compounded formulas are listed below in Section 13.

Due to the broad-scale, survey nature of this study, a large participant population is expected. As we are not conducting a double-blind study with the use of controls, sample sizes are drawn from the literature that have used retrospective survey of the efficacy and tolerability of analgesics.

With respect to variables that have been suggested to affect skin permeability (see Background), we anticipate drawing from populations that vary in individual and environmental differences.

Individual differences will include:

- Participant sex (male or female)
- Participant race (White, Black, Asian, Hispanic)
- Pain condition diagnosis (neuropathy, inflammatory pain, fibromyalgia, post-surgical pain, other chronic pain condition, other acute pain condition)
- Affected body areas
    - Axial:
        - Neck
        - Spine
        - Hips
        - Knees
        - Shoulders
        - Elbow
        - Lower back
        - Chest
        - Abdomen
    - Extremities
        - Hand/wrist
        - Foot/ankle

Environmental differences will include:

- Climate (as related to humidity and temperature) will be assessed for various large North American areas.

- Semi-arid climate
- Humid subtropical
- Marine
- Mediterranean-like climate
- Humid continental climate
- Mountain climate
- Tropical
- Desert

Other factors that will be examined:

- Composition of prescribed compounded cream
- Amount/dosage of compounded cream used
- Simultaneous use of other analgesics/medications
- Length of time prescribed the compounded cream
- Length of time prescribed other analgesic medications to treat the pain condition

Based on these broad differences/variables, we anticipate recruiting from a large, heterogeneous population with varied treatment conditions. Given that topical analgesic literature in the survey/chart review field often draw conclusions from groups as small as 20 to 30 participants[7] to initial cohorts of more than 100 participants[28], there are a number of variables that affect attrition/dropout rate. Clinical studies focusing on these dropout rates over multi-year observational studies have found rates ranging from 30%[29] to greater than 92% in some cases[30]. In order to provide ourselves with the greatest amount of information in this observational study and to obtain the statistical power necessary for this multivariate investigation, we anticipate recruiting as many as 300,000 participants over a 5 year time frame, with the understanding that a divergent (and potentially) large rate of participant drop-out is to be expected. We believe that this will provide us with the most accurate representation of the varied populations.

Healthcare providers will assign a unique number to each participant that is independent of any identifiers. No identifiers to participants will be collected or made available to those assimilating the data. Each PI will be assigned a site number. The PI will assign sequential numbers to subjects enrolled and include the site number in the identifier.

4. Study procedures:

Healthcare providers in outpatient centers and private practices of the desired regions within the United States will be advised of the goals of this study to survey patients who fall within the inclusionary criteria who are presently diagnosed with pain conditions and who would be prescribed a compounded analgesic ointment during the normal course of routine pain management. They will advise prospective participants of the study's goals and time requirements. The patient's sex, age, race, height, weight, pain condition diagnosis, affected body area, geographical climate/region of the patient's home/treatment center, and current use of other analgesics will be noted. The frequency and location of application will also be recorded.

Upon returning for subsequent visits to the health center, the effectiveness of the topical ointment preparation will be evaluated based on dichotomous scales to evaluate meaningful pain relief in retrospective surveys of pain treatments (hence minimizing any potential influence in patient diagnosis, treatment, or outcome)[7,31].

"Meaningful" relief was defined when at least 1 of the following was found:

A. Significant changes in any of multiple quantitatively measured outcomes, for

example, VAS score, specific questionnaire, or percentage of pain relief;

B. "Satisfactory" or "acceptable" pain relief as deemed by the patients or healthcare providers;

C. "Worthwhile" relief obtained through narratives; for example, pain relief of 30% or greater from baseline, concurrent improvement on various dimensions (pain, function, fewer side effects, return to work, etc.)

"Nonmeaningful" relief was defined when at least 1 of the following occurred:

A. Relief less than 30% of pain reduction (this percentage was arbitrarily agreed upon by the authors of this present study);

B. "Mild" or "no" relief of the original pain, as deemed by the patients or healthcare providers.

C. Discontinued use of drug for reasons such as inability to pay, loss of insurance, adverse effect, loss of access to medication.

Additionally, we will obtain measures of the "maintenance" of pain relief over time; for example, a measure of weeks over which the patient attainted "satisfactory" pain relief as deemed by the patients or healthcare providers.

Healthcare providers will be advised on the study's goals of evaluating the efficacy of the compounded topical medications in a variety of pain conditions that could be affected by individual and environmental variation. We do not intend to influence the length of the participants' treatment and simply require the occurrence of at least one subsequent follow-up visit to assess meaningful pain relief. Participants will be encouraged to keep daily journals and may opt to use a study-specific online portal in order to track their degree of pain relief over time. These self-reports will also be reviewed with healthcare providers at each follow-up visit during the duration of the study. At least one follow-up visit is required.

In collecting this broad data-set, given the range of pain etiologies and environmental factors being examined, data collection is expected to continue up to 2 years after enrollment has concluded.

The age range, median age, number of females, number of males, race, geographic region, pain diagnosis, affected body area, and current analgesic prescriptions and dosages will be recorded to provide an estimate of the these for each population.

The effectiveness of the topical cream will be evaluated as the number of patients with improvement (n), defined as having "meaningful" relief[31], compared to the total number of patients receiving the prescription for the compound (N). In this manner, the percentage of patients with meaningful relief while prescribed the compound can be evaluated. The broad nature of this data survey will allow us to further distinguish discrete subsets for comparison (e.g., men with lower back muscle pain, living in semi-arid zones finding relief compared to similar participants living in more humid climates).

At initial and follow-up visits, participants will complete a brief pain interview administered by their healthcare provider based on the short form of the McGill pain assessment questionnaire[32], a well-established paradigm which has been recommended for use in neuropathic[33] and lower back pain studies[34], among other conditions. This paradigm offers several advantages in that quantitative assessments of the kind of pain are selected by participants, providing a metric of descriptors of types of pain that can be compared in subsequent visits. Furthermore, a visual analog scale (VAS) and present pain index (PPI) are

included, as these have been noted to provide complimentary assessments of pain intensity[34]. Additional questions will be drawn from the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) Pain Scale and Neuropathic Pain Diagnostic (DN4) questionnaires, which focus on discerning neuropathic vs. nociceptive pain characteristics in patients[35,36].

A copy of an example pain assessment template is attached. Briefly, the participant and healthcare provider will select among the 15 pain descriptors (e.g., throbbing, shooting, stabbing) and then select a corresponding level of intensity of the descriptor. The VAS provides a complimentary assessment of pain intensity, as the participant is instructed to draw a line on a 100 mm range between "no pain" and "worst pain." The PPI assesses the overall intensity of pain, regardless of the descriptor/subtype of pain. Each of these values can be totaled and compared across subsequent follow up visit. The entire test is expected to take approximately 5 minutes to complete. In addition, participants may opt to complete these pain assessment surveys in a dedicated, secure online portal with assistance of their healthcare provider. Data submitted via this secure online portal will be protected by online encryption algorithms to ensure patient data is kept confidential. This is at the discretion of the principal investigator/healthcare provider.

Participants will be removed from the study if they choose to no longer participate or as advised by their healthcare providers. As their routine course of treatment (as evaluated by their healthcare providers) will not be affected by their participation, there is not expected to be a failure in treatment.

As we are gathering data regarding the effectiveness of the compound in pain treatment as determined by the healthcare provider, the routine course of pain condition treatment (as evaluated by the healthcare providers for participants) is not expected to change following the end of the data collection period.

All participants will be under the normal supervision of their healthcare provider/pain care specialist throughout the duration of the study.

5. Data Analysis Strategy

The data collected in this naturalistic experiment will be utilized to assess the efficacy and safety of treating pain conditions with commonly-prescribed compounded topical formulas. As a naturalistic experiment, we have not included a control scenario or taken any steps to modify the typical course of treatment for any participant in the study. Therefore, there will be a variety of treatment conditions represented in the data, such as different ingredient concentrations and lengths of therapy, as well as interindividual and environmental differences between participants such as race and gender of patients living in regions that vary in terms of climate, etc. (See Section 3 for a list of example variables). Treatment variables, interindividual variables, and environmental variables will be tested via linear mixed models to determine their impact on pain condition symptomatology (as assessed by the administered pain questionnaires) and on safety (as reported by the PI's). All statistical tests will be two-sided, with an alpha level of 0.05, and false discovery rate will be used to adjust the cutoff for significance. Statistical computations will be performed with SPSS Version 19 (IBM, Armonk, NY).

6. Data Custody, Security and Protection of Subject Confidentiality

Healthcare providers will maintain all confidential and protected information. Healthcare providers will assign a unique number to each participant that is independent of any identifiers.

No identifiers to participants will be collected or made available to those assimilating the data or provided to any other employees at the sponsoring organization. The sponsor's employees will not be able to access the pharmacies' records, neither electronically nor physically. The computers used by those assimilating the data will not have access to pharmacy records, nor will the individuals have access to any protected health information.

The pharmacy staff, including but not limited to the pharmacists and pharmacy technicians, will not have knowledge of which prescribers are PIs in the study nor will they have knowledge of which patients are participants in the study. Therefore, only the patients' healthcare providers will be aware of which of their own patients are involved in the study.

7. Recruitment process:

Healthcare providers likely to be treating patients of varying pain conditions will be contacted regarding the intents of the study. From their patients who meet the study criteria and who are prescribed topical analgesic compounds, healthcare providers will voluntarily inform potential participants of the nature of the study, the expected time commitment, and collected data information.

8. Consent process and documentation:

First, healthcare providers who are currently treating patients with pain conditions will be approached to act as Principal Investigators (PIs) for the study. The basic premises of the study will be provided.

Next, Principal Investigators will obtain the consent of patients diagnosed with a pain condition who have been or will be prescribed a topical analgesic compounded medication as part of their standard course of treatment (independent of the recruitment phases of this study).

The PI or qualified site staff will conduct the consent process in a private room. The person conducting the consent discussion will discuss the study and be available for any questions. The potential participant will also be able to discuss this study and their potential participation with other individuals. The potential participant will not be pressured to sign the consent form during this process. The participant may choose to join the study after this consent process by contacting the PI and requesting a meeting to undergo the consent process after careful consideration.

Consent forms will be signed and dated by both the subject and the person conducting the consent discussion. A signed and dated copy will be provided to the subjects.

All consent forms will be collected and maintained by the Principal Investigator at each site. A copy of the consent form will be sent to the sponsor along with the first pain assessment questionnaire.

9. Audit:

Sponsor's employees will randomly audit sites for compliance with the protocol. Data and consent forms will be reviewed but not removed from the site.

Each week, the Sponsor will email all sites to maintain open lines of communication throughout the study. This email will ask each PI to respond, stating that they are following the

protocol. Each PI will also be able to address any concerns or questions to the Sponsor at this time. The PIs will also have direct access to the Sponsor should any issues arise that require immediate attention.

Each month all PIs will attend a real-time, on-line video meeting. This meeting will address any issues or questions that have arisen during the last month. This session will also enable the PIs to share experiences with others.

Sponsor will have an employee visit each site at least once a year for an on-site audit. As the number of sites grows, the Sponsor will add employees to be able to adequately monitor the sites. Each on-site audit will include review of consent forms, review of protocol, and a personal meeting with the PI to address any concerns.

10. Risks:

This study seeks to evaluate the effectiveness analgesic compounds that would ordinarily be prescribed to participants, as evaluated by their healthcare providers, regardless of the presence of the study and data collection steps. In light of this, we expect no physical, psychological, emotional, social, legal, or economic risks for any participants.

We do not expect any adverse reactions or harm of any extent to occur due to the study, as the participants will be following the normal course of pain treatment as advised by their healthcare providers.

Healthcare providers will be expected to expend the time necessary to properly evaluate whether or not to participate in the study (variable), review lists of potential participants among their own patients (variable), discuss the study's goals with patients/potential participants (variable), and record data regarding the extent of meaningful pain relief obtained during the course of the study over follow-up visits (expected to be 5 to 10 minutes).

Patients will be expected to expend the time necessary to properly evaluate whether or not to participate in the study (variable), discuss the study's goals with healthcare providers (variable), and provide data regarding the extent of meaningful pain relief obtained during the course of the study over follow-up visits (expected to be 5 to 10 minutes) as well as self-reports regarding pain relief (daily journal; expected to be <1 min). Self-participation on the online study portal questionnaire is expected to require 5 to 10 minutes per week for each participant.

Evaluation of participants and their degree of meaningful pain relief will be evaluated solely by the participants' own healthcare providers and will follow all appropriate HIPAA laws related to privacy. Sensitive information will not be collected for data analysis.

Although allergies to any of the medications in this formula are rare, the following could occur: rash, hives, itching, swelling of the application area, redness, irritation of the application area.

12. Benefits:

Participants are to receive the standard degree of care that they would receive from their healthcare providers for their pain conditions and have the normal expectations of medical treatment for these conditions.

These data are expected to provide a novel, uncommonly large degree of information regarding the effectiveness of commonly used analgesic compounded medications in a wide variety of populations, differing in individual differences (e.g., sex, race, gender, diagnoses, affected body regions) as well as environmental differences. Thus, one of our future goals includes more targeted approaches of beneficial analgesic compounds to discrete subsets of patients that appear likely to respond well to compounded medications. When appropriate, we will disseminate information regarding these compounds to healthcare providers treating patients with pain conditions via peer-reviewed scientific articles.

13. Payment:

Participants will be paid fifty dollars ($50) per month to participate in the study. Participants will be mailed a pre-paid visa gift card (or its equivalent) at the end of each month. This will continue until the participant drops out of the study or their medical provider decides that the treatment is no longer needed and/or appropriate for that specific participant.

There will be no consequences for not completing all phases of the research.

14. Safety and Efficacy of Active Pharmaceutical Ingredients:

The dosages and active pharmaceutical ingredients for the commonly-prescribed formulas below are suggestions and serve only as further information for the clinician when determining the necessary prescription:

Common Formula 1: Ketamine (15%), Gabapentin (6%), Prilocaine (7%), Baclofen (3%), Diclofenac (2%), Clonidine (0.2%)
Common Formula 2: Flurbiprofen (10%), Gabapentin (6%), Baclofen (3%), Clonidine (0.2%)
Common Formula 3: Lidocaine (5%), Topiramate (3%), Meloxicam (0.3%)
Common Formula 4: Gabapentin (6%), Cyclobenzaprine (1%), Lidocaine (1.83%), Prilocaine (1.83%), Meloxicam (0.2%)
Common Formula 5: Tramadol (5%), Duloxetine (1%), Meloxicam (0.2%)

The formulas listed above can be compounded utilizing a variety of lipophilic creams commonly used by compounding pharmacies to improve skin penetrance (for example, Lipopen Ultra from Freedom Pharmaceuticals).

Drug management is provided solely by the patients' healthcare providers, as part of the patients' routine course of treatment for their pain conditions. Compounded topical medications will be prepared and dispensed by a licensed compounding pharmacy per a healthcare provider's written prescription order.

Any pharmacy may be used to fill the participant's medication for purposes of this study as long as they are preapproved by the sponsor, in writing, prior to participation. The study sponsor will ensure that all approved pharmacies follow identical standard operating procedures for compounding each topical medication in the study.

The PI will fax a prescription order to a compounding pharmacy. Once the compounding pharmacy receives a valid prescription order from the PI for a specific patient, it will begin compounding the medication. The medication is then shipped directly to the patient's home address.

The PI will provide the sponsor with the collected questionnaires on a monthly basis. The PI will be able to fax or scan and email the questionnaires to the sponsor. Alternatively, participants may submit questionnaire information through the designated online study portal. Study sponsors will keep the information confidential and secure.

15. Safety monitoring:

Patient safety will be assessed at every follow-up visit to the prescribing healthcare provider as part of their normal course of treatment.

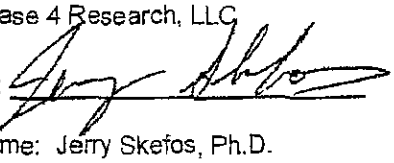
We do not seek to interfere with the routine treatment that the patients would be receiving from their healthcare providers. Therefore, it is at the discretion of the healthcare provider to terminate the use of any compounds under investigation or to alter the treatment schedule.

16. Plan for reporting unanticipated problems/adverse events:

Any unanticipated events as assessed by the healthcare provider will be reported via the online study portal to the sponsor, who will report these to the IRB within ten (10) business days from the date the sponsor became aware of the unanticipated problem. Abuse or illegal activity will be reported to appropriate government and regulatory agencies immediately.

Sponsor signature page approving final version

Sponsor:
Phase 4 Research, LLC

By: 

Name: Jerry Skefos, Ph.D.
Title: President
Date: 11/4/14

PI Signature Page

Principal Investigator:

By: _____

Name: _____

Date: _____

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